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January 1978

THE BRITISH JOURNAL OF RADIOLOGY

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X-ray diagnosis
Radiation oncology
Nuclear medicine
Ultrasound
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Radiobiology
Radiation protection
and related disciplines

Published b
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The British Journal of Radiology

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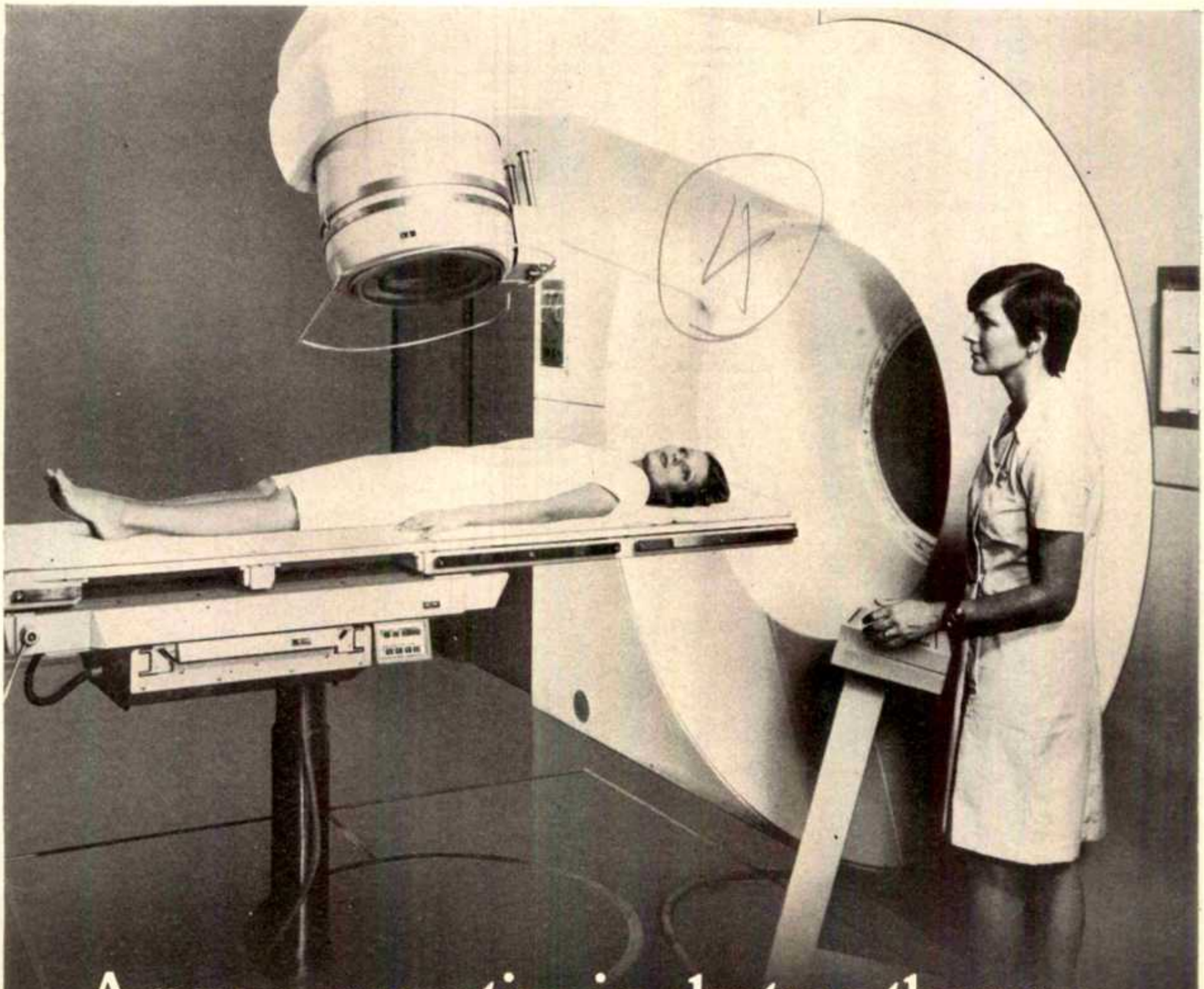

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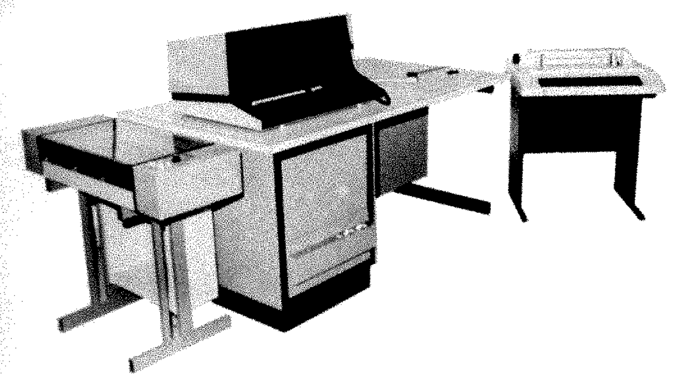

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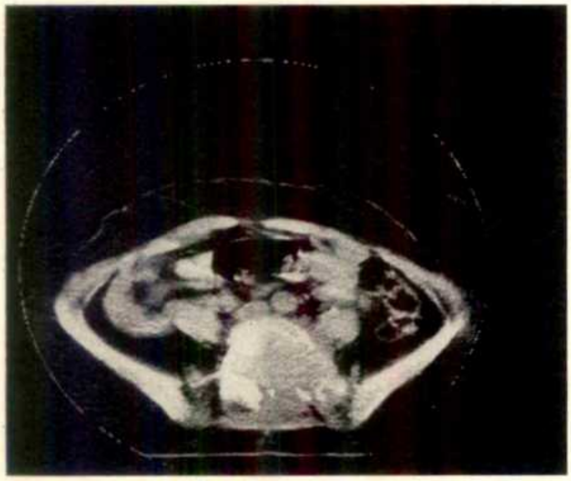

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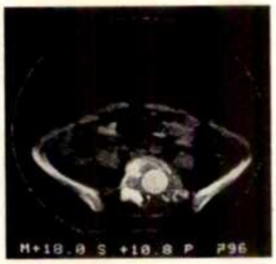

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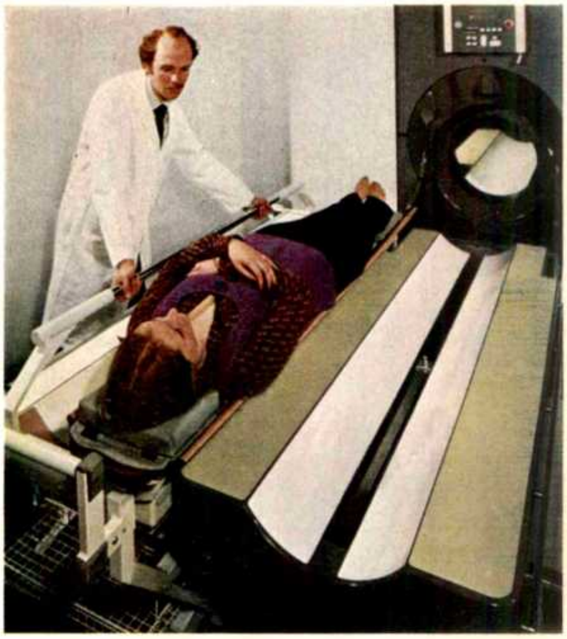

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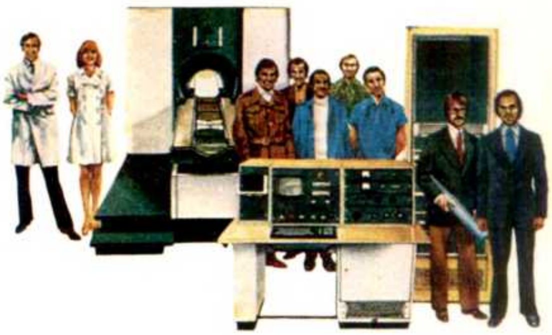

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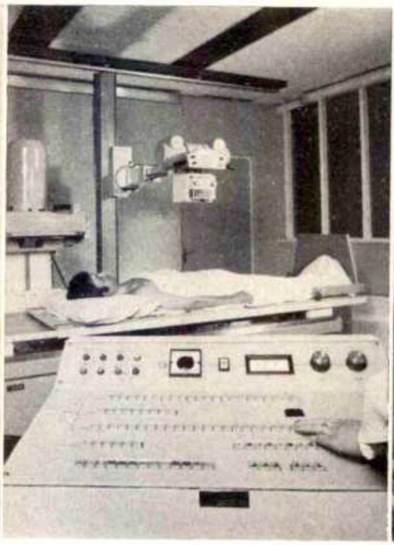

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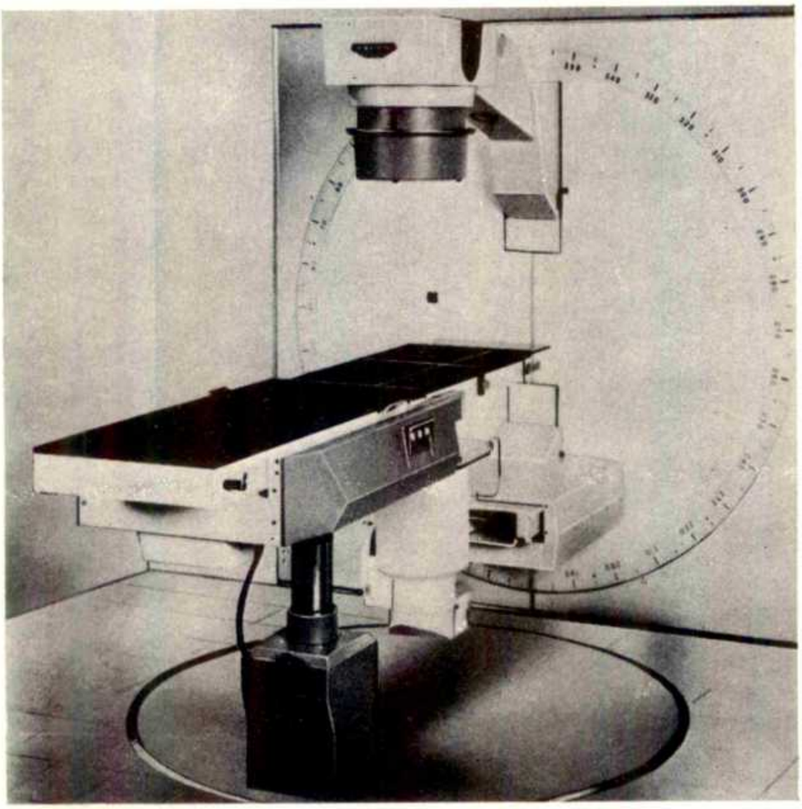

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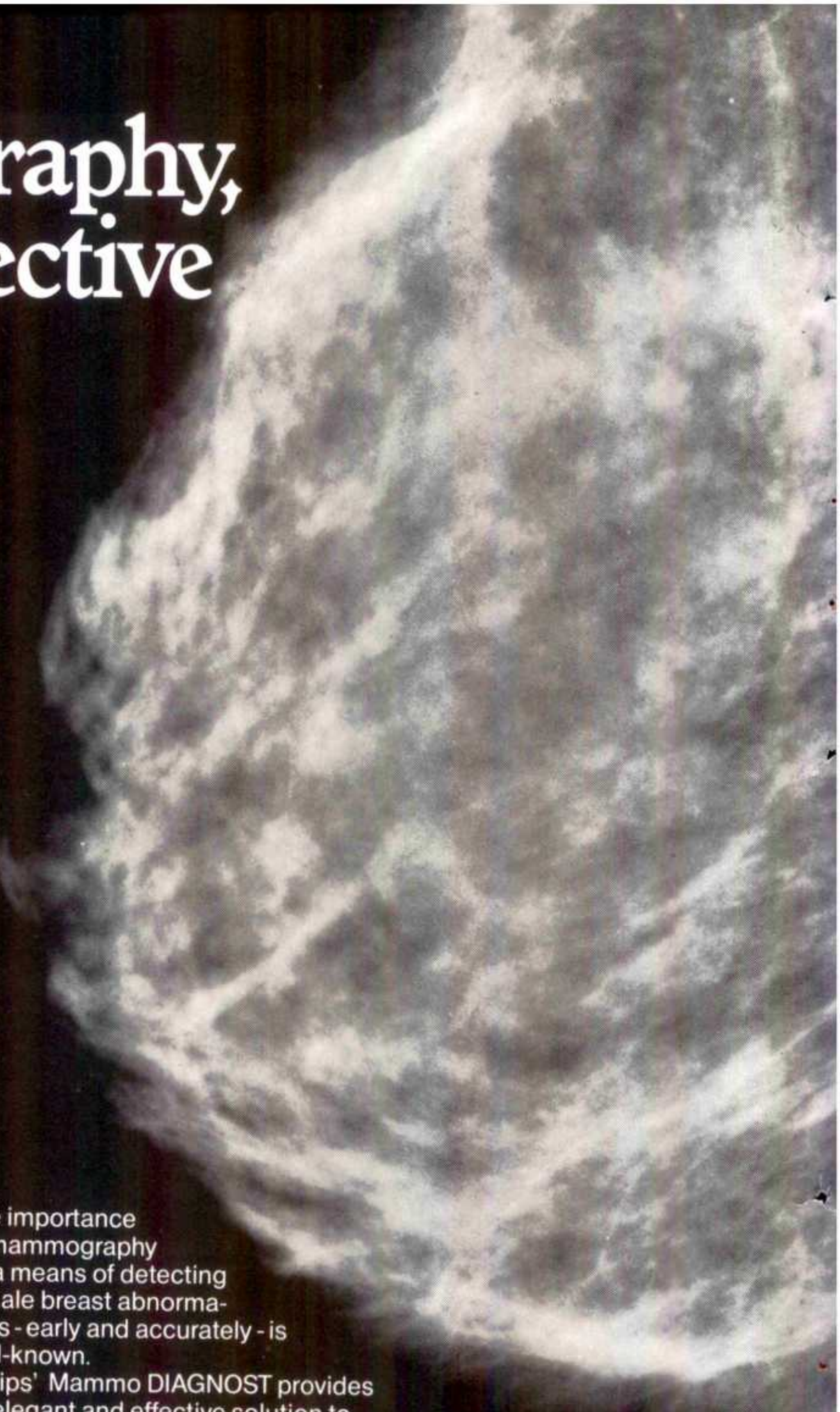

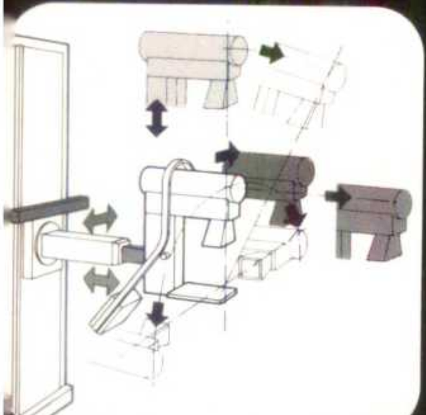

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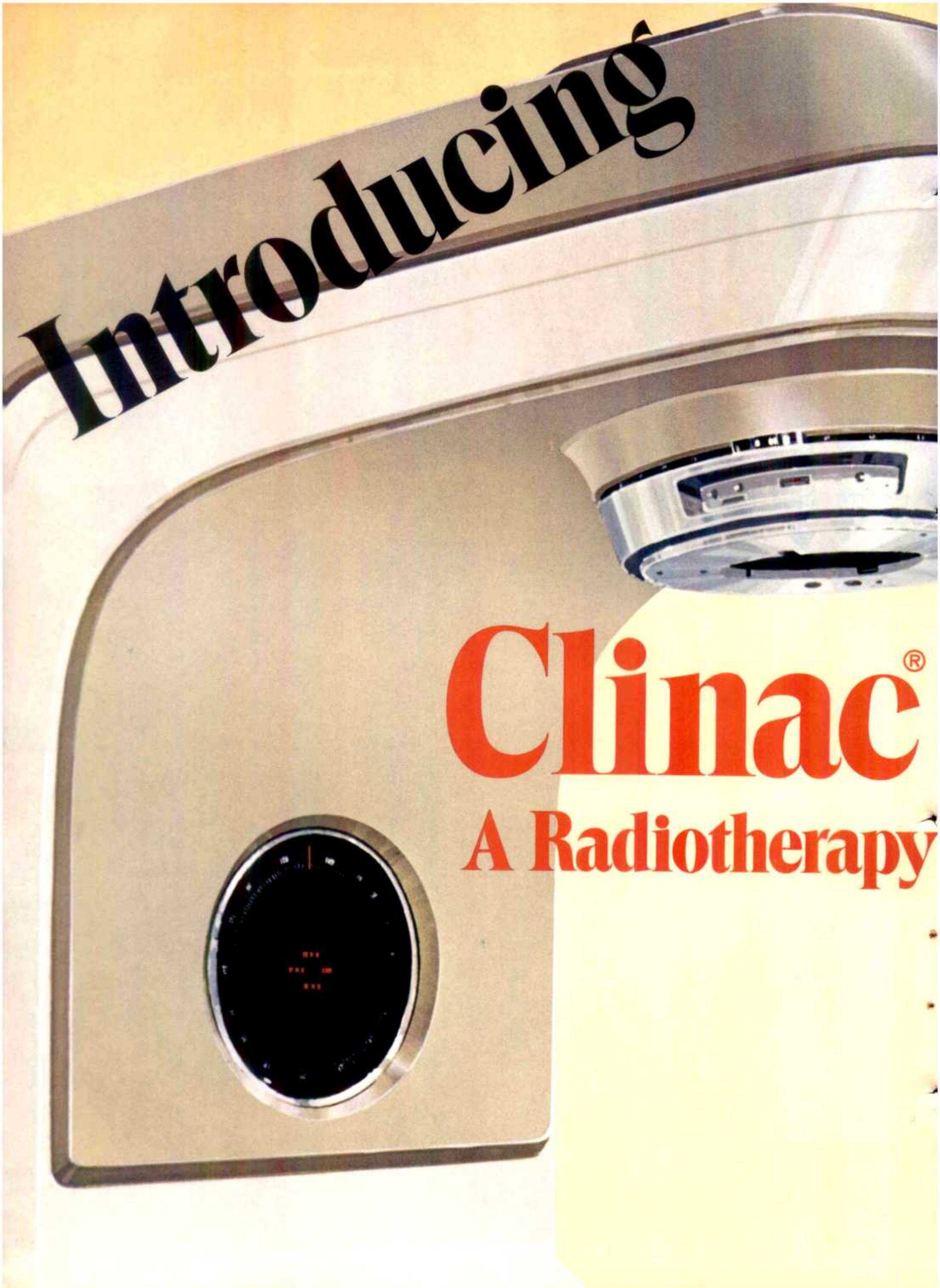
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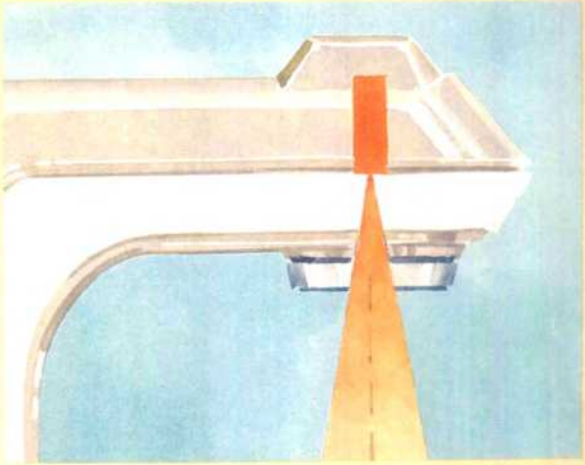

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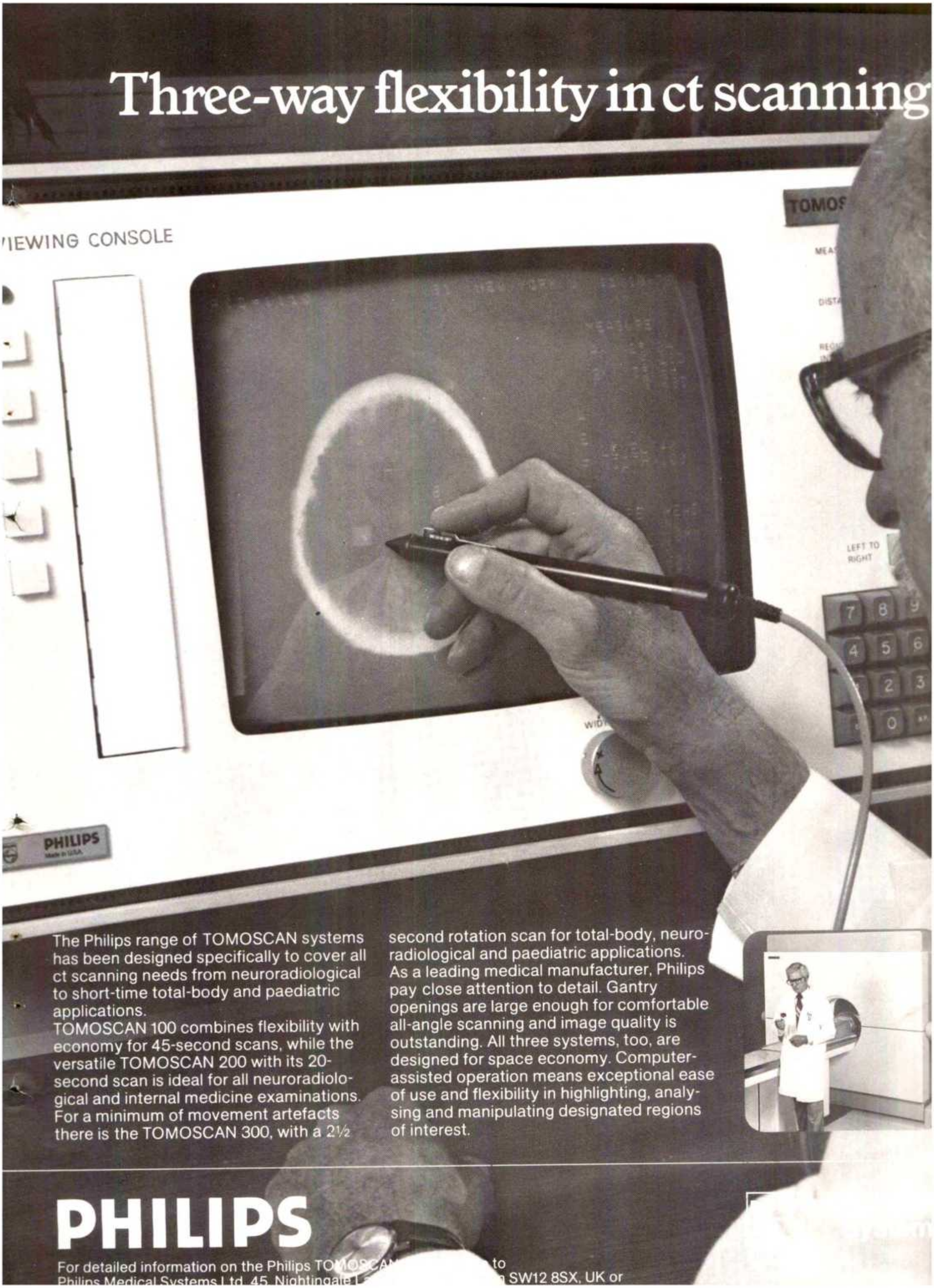

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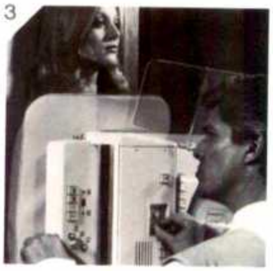

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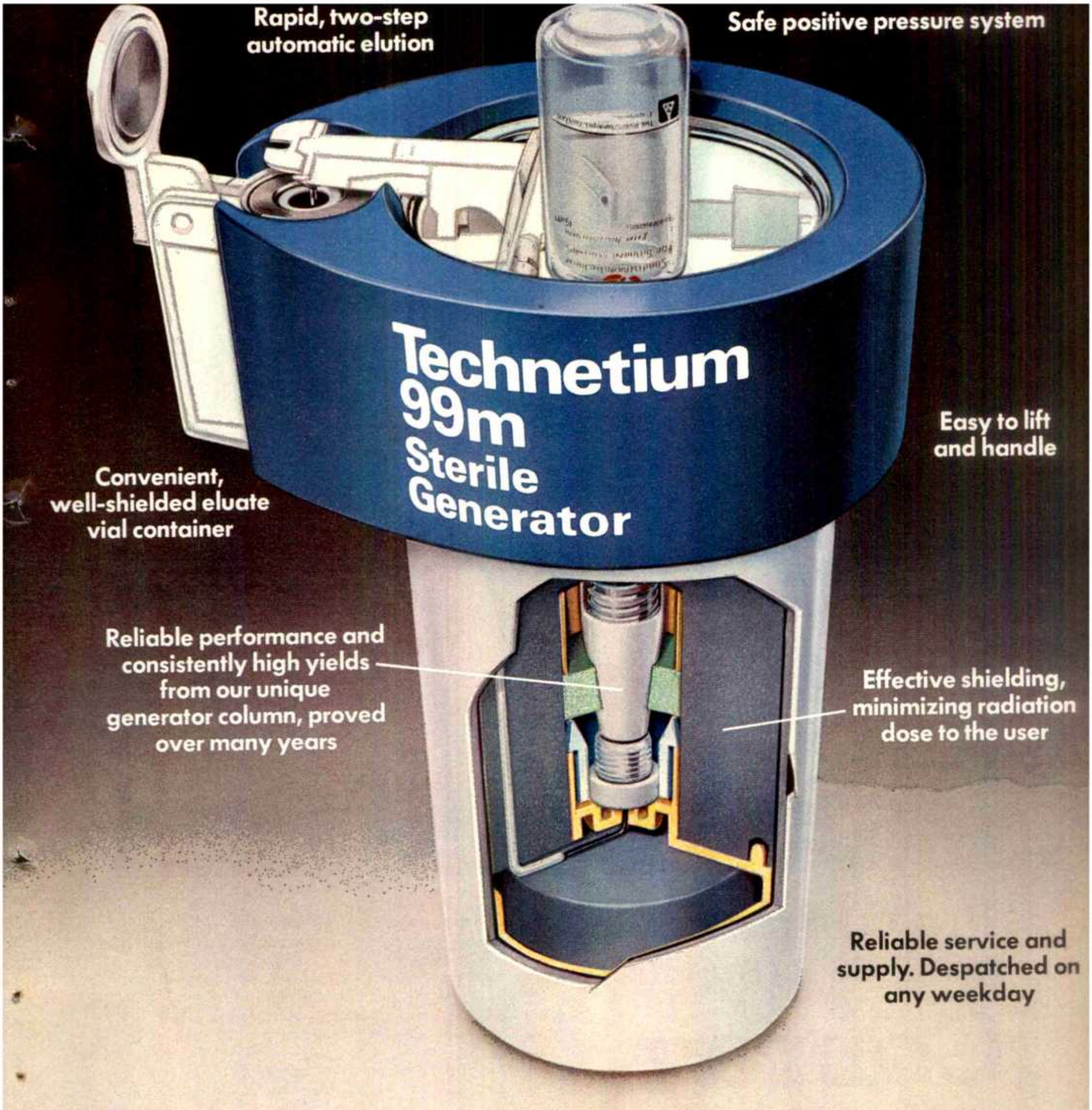
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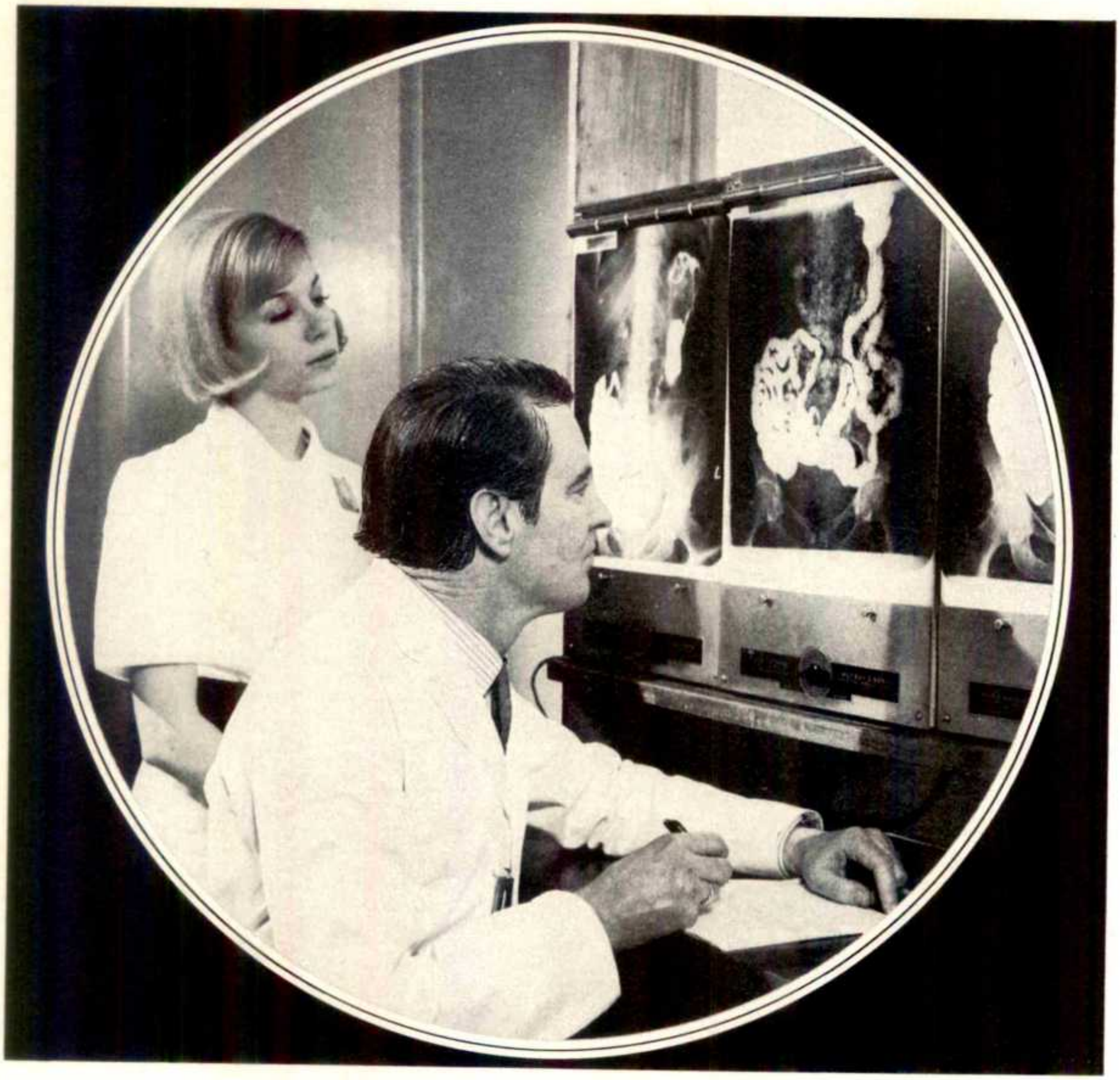

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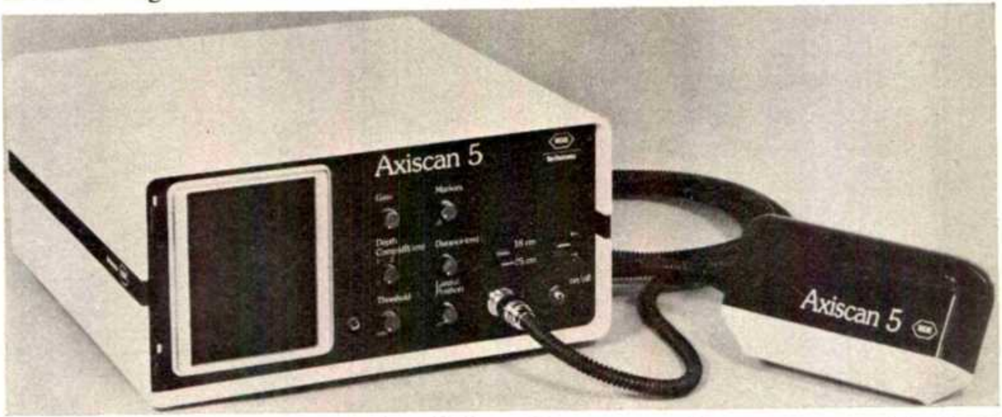

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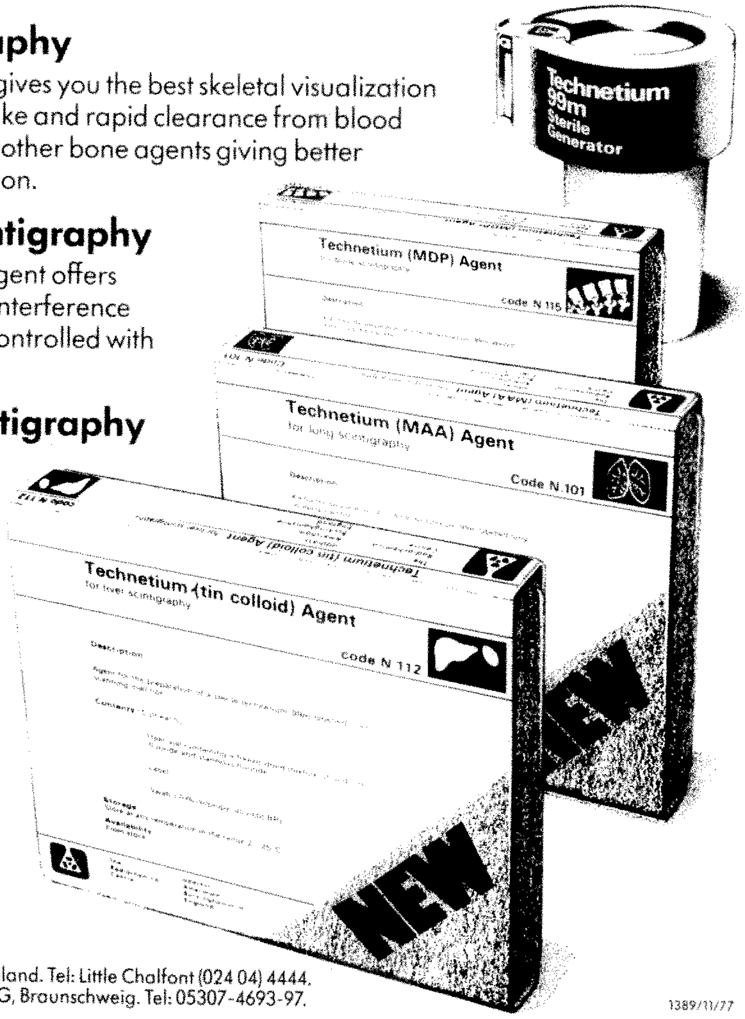

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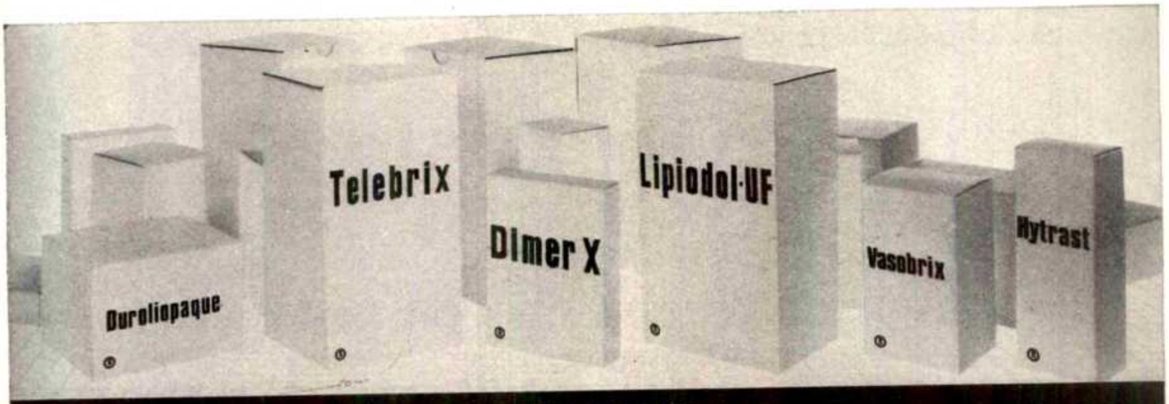

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The Pathogenesis of Reflux Nephropathy

**By Professor C. J. Hodson, F.R.C.P., F.R.C.R.,
T. M. J. Maling, M.B., B.Ch., M.C.R.A., F.R.C.R.,
P. J. McManamon, M.B., B.Ch., L.G.M.C., F.R.C.R. and
M. G. Lewis, M.B., B.S., M.D., M.R.C.Path.**

The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

These observations have been given a firm experimental basis by Professor Hodson and his associates. Their careful work on the growing pig has shown that the sites of intra-parenchymal or intra-renal reflux (I.R.R.) are the sites of subsequent scarring and atrophy. I.R.R. only occurs above a critical pressure level; reflux at lower-pressures produces no evident damage. Infection aggravates scarring, but in the presence of I.R.R., scarring can occur with sterile urine.

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The British Journal of Radiology

Computed tomography in pancreatic disease

By R. A. Fawcitt, M.B., Ch.B., D.M.R.D., F.R.C.R., W. St. C. Forbes, M.A., M.B., D.R.C.O.G., D.M.R.D., F.R.C.R.,* I. Isherwood, M.B., Ch.B., D.M.R.D., M.R.C.P., F.R.C.R.

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(*Received July, 1977*)

Abstract

Computed tomography (CT) of the pancreas has been evaluated in 50 patients with established exocrine pancreatic disease and 20 patients without pancreatic disease.

Increase in size, irregularity in outline and heterogeneity of composition of the pancreas implied disease but were in no way specific to any particular disease entity. In acute pancreatitis, following complete resolution, the pancreas appeared normal whereas incomplete resolution was associated with non-specific swelling and heterogeneity of density. The extent and location of pseudocysts could be accurately delineated. In chronic pancreatitis, duct calculi, duct dilatation and large intrapancreatic cysts aided the differentiation between focal enlargement due to chronic pancreatitis and expansion due to cancer. Hepatic metastases and abnormalities of the biliary system seen in association with cancer further aided this differentiation.

Following the development of CT as a method of neuroradiological investigation, this non-invasive technique of horizontal section tomography has been extended to cover the whole body. Several studies (Alfidi *et al.*, 1975; Haaga *et al.*, 1976; Kreel, 1977; Sheedy *et al.*, 1976; Stanley *et al.*, 1976; Wiggans *et al.*, 1976) have indicated that the pancreas can be delineated.

This study is an assessment of the CT appearances of the normal pancreas and of the changes associated with established pancreatic disease. Such observations are a prerequisite to a further planned prospective study of CT in the management of pancreatic disease.

Materials and Methods

All patients have been investigated with the EMI whole body scanner (CT5000) situated in the Department of Diagnostic Radiology, Medical School, University of Manchester, using the fast scan mode (20 seconds).

Fifty patients with pancreatic disease have been examined. Nine had a diagnosis of acute and relapsing acute pancreatitis and were examined 1–12 weeks after the clinical attack. Thirty patients had a diagnosis of chronic pancreatitis and were subdivided on clinical grounds into: (a) relapsing chronic pancreatitis; (b) silent chronic pancreatitis (in which pain was never a feature); (c) patients with constant pancreatic pain for more than 12 weeks.

Eleven patients with cancer of the pancreas were examined either to establish the diagnosis or for follow-up examination after surgery.

The CT appearances of the normal pancreas were evaluated in 20 patients; ten in whom pancreatic disease was suspected but finally excluded and ten undergoing investigation of the upper renal tract.

All patients were examined in the supine position and a number in the right lateral decubitus position. The latter was of value in the determination of pancreatic mobility and accurate location of the pancreatic head.

Bowel paralysis was obtained with Propantheline, 30 mg i.v. injection. Variation in the level and obliquity of the pancreas necessitated several adjacent sections to delineate the length of the organ.

TABLE I

CT appearance	Pancreatitis Chronic	Pancreatitis Acute	Cancer
Normal	4	1	1
Abnormal	26	8	10

---

*Research Fellow in Diagnostic Radiology supported by a grant from EMI Medical Ltd.

TABLE II

CT abnormal features General	Pancreatitis Chronic $n=30$(%)	 Acute $n=9$ (%)	Cancer $n=11$ (%)	Normal $n=20$ (%)
Size				
Reduced	4 (13)	0	0	2 (10)
Increased	12 (40)	4 (44)	7 (64)	1 (5)
Irregular outline	18 (60)	5 (56)	7 (64)	2 (10)
Heterogeneous density	12 (40)	5 (56)	5 (45)	4 (20)
Loss of mobility	6/17 (35)	—	1/3 (33)	—
Obliteration of retropancreatic space	4 (13)	0	2 (18)	—

TABLE III

CT abnormal features Detailed	Pancreatitis Chronic n (%)	 Acute n (%)	Cancer n (%)	Normal
Localized swelling	9 (30)	1 (11)	9 (82)	—
Duct calculi	11 (33)	—	—	—
Duct dilatation	14 (47)	2 (22)	—	—
Intrapancreatic cyst	4 (13)	—	—	—
Extrapancreatic cyst	—	2 (22)	—	—
Hepatic metastases			4 (36)	—
Dilated bile ducts			4 (36)	—

Some sections were repeated after oral contrast (Gastrografin 5%) or i.v. contrast (100 ml Conray 420) or both.

RESULTS

Visualization of the pancreas or pancreatic region was of diagnostic quality in all but one patient. No CT abnormality could be detected in six of the 50 patients with established pancreatic disease (Table I).

The features observed are tabulated in Tables II and III. The size of the pancreas was evaluated by noting the ratio of the A.P. diameter of the pancreatic body and the A.P. diameter of the adjacent vertebral body. A ratio of less than one-third was considered small and above two-thirds large.

DISCUSSION

The normal pancreas (Fig. 1) was usually of homogeneous density similar to that of liver and spleen and of smooth outline but occasionally showed fine mottling (2/20) or fine crenation of contour (4/20). The ratio between the A.P. diameter of the gland and the A.P. diameter of the adjacent vertebral body was 0.5±0.11 (Mean ±2 S.D.). The retropancreatic fat space was well demarcated and the superior mesenteric artery always definable in this space.

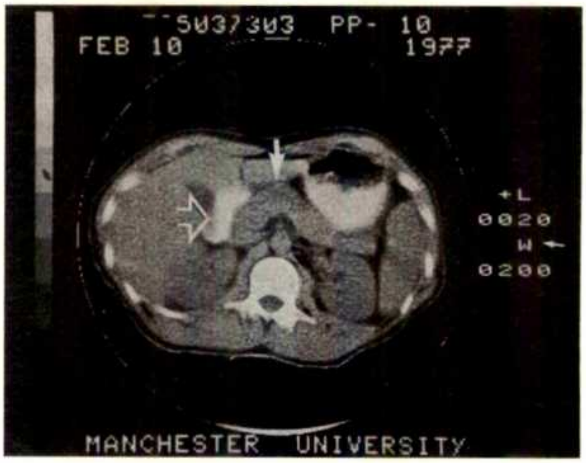

FIG. 1.

Normal pancreas (↓). Gastrografin in stomach and duodenal loop (→).

Increase in size, irregularity in outline and heterogeneity of density of the pancreas imply disease but are not specific to any particular disease entity.

Following acute pancreatitis the appearances at CT varied with the extent of clinical recovery. When recovery was complete the pancreas appeared normal, when incomplete a swollen, irregular pancreas

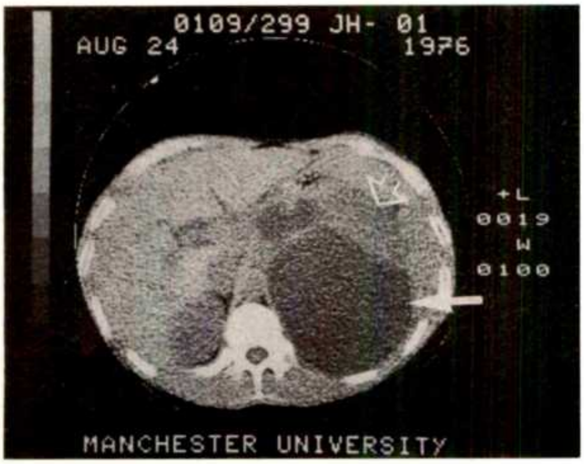

FIG. 2.

Bilocular pancreatic pseudocyst of low density (←). Left kidney displaced anteriorly (↓).

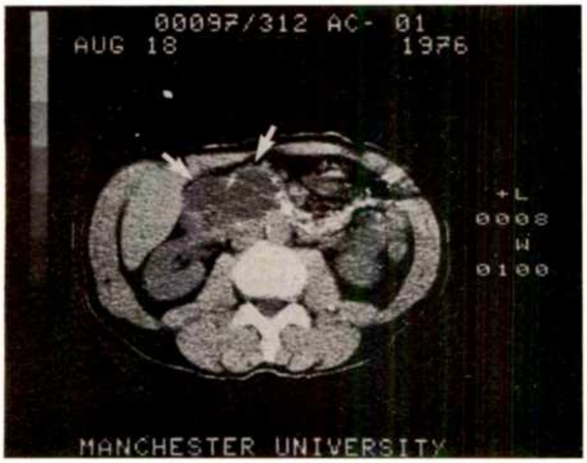

FIG. 3.

Two paraductal intrapancreatic cysts (↓) expanding and deforming the head of the pancreas. Note calcification within the pancreas.

of heterogeneous density was observed. The extent and location of pseudocysts (Fig. 2) in relation to adjacent viscera were readily identifiable.

CT was abnormal in 27 of 30 patients with chronic pancreatitis. Of the three patients with normal scans one subsequently had a distal pancreatectomy with confirmation of chronic pancreatitis and two patients with abdominal pain had severely impaired pancreatic exocrine secretion and subsequently developed diabetes. The diagnostic features of chronic pancreatitis were duct calculi, dilatation of the main pancreatic duct and paraductal cysts which significantly deformed the surrounding parenchyma (Fig. 3). For two patients in clinical remission but with large paraductal cysts, discovery of the cysts was a valuable contribution to management. In a disease which progresses inexorably to destruction of pancreatic tissue the size of the pancreas would not be expected to increase even during a clinical relapse and indeed may even be reduced. CT abnormalities in silent chronic pancreatitis were generally similar to those in relapsing chronic pancreatitis with the exception that none of the eight patients examined had a large paraductal cyst. All four patients with relentless abdominal pain had a mass in the head of the pancreas which contained cystic or calcified areas. These findings were confirmed at operation which was required for the relief of the pain.

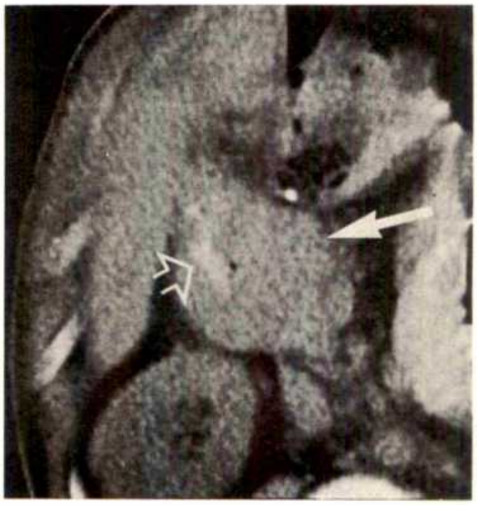

FIG. 4.

Recurrent carcinoma of the ampulla of Vater (←). Note annular deformity of contrast-filled second part of the duodenum (→). Patient in the right lateral decubitus position.

Cancer of the pancreas commonly produced a solid localized mass of varying density (nine of 11 patients) with gross distortion of local anatomy and loss of definition between pancreas and contiguous viscera (Fig. 4). Absence of features specific to chronic pancreatitis (in which focal enlargement of the gland was also seen in seven of 30 patients), associated abnormalities of the biliary tree and the presence of metastases in the liver or para-aortic nodes further aided this differentiation. The CT scan was normal in one patient with a Zollinger-Ellison syndrome who was found to have a gastrinoma at laparotomy.

Conclusion

It is apparent that some of the radiological features of the pancreas as seen on the CT scan are non-specific but some characteristic features are readily detectable. These features may be of value not only in the differentiation of diseased from normal pancreas but also in the definitive diagnosis of the disease process.

Acknowledgments

The authors would like to thank the radiographic and photographic staff of the University Department of Diagnostic Radiology for their valuable support. They would also like to express gratitude to Mrs M. Tipton for expert secretarial assistance.

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Book review

Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in Radiotherapy Procedures, ICRU Report 24, pp. vii+67, 1976 (Washington, ICRU Publications), $6.

Report 24 is the second of a group of three which collectively supersede Report 10d on *Clinical Dosimetry* (1963). (Report 23 (1973) dealt with absorbed dose in a water phantom under well defined conditions of irradiation.) Report 24 (1976) deals with the transition from phantom dose to patient dose under conditions of clinical irradiation. It opens with a comprehensive review of terminology and current practice in obtaining and presenting basic data from water phantom measurements, overlapping considerably with ICRU 23 in the interests of completeness. The next chapter on patient data describes present methods of obtaining contours and cross-sections, and emphasizes the inadequacy of the anatomical information frequently used as a basis for treatment planning. The brief mention of computerized tomography leaves an uneasy feeling that this chapter will be quickly outdated by the impact of CT scanning. Three alternative methods of allowing for oblique incidence are described in the chapter on combination of basic and patient data, which also considers compensation for body inhomogeneities and cavities. After two pages of elementary "do-it-yourself" instruction on the technique of manually combining single beam isodoses, I found the following statement rather odd: "The procedures described in the preceding section are independent of the nature and even the existence of a patient". On the contrary, the procedures assume that the patient is present and is water equivalent. The presentation of dose distributions in the unusual form of scaled down "plateau diagrams" in idealized quasi-elliptical patients is developed at length, rather out of proportion to its usefulness in real treatment planning. The section on computation for rotation or arc therapy ends with some penetrating comments on the limitations of the resulting dose distributions, but surprisingly fails to mention the use of wedges to overcome the limitations. Compensating filters are particularly well reviewed in the chapter on planing and delivery of radiation therapy, which also includes a plea for more *in vivo* dose measurements. In the last section the authors have done a valuable service by gathering together the published facts in the very important but hitherto neglected area of inaccuracies in clinical dosimetry caused by mistakes of all kinds at all stages of the radiotherapy treatment flow chart. Their conclusion that even in "careful" centres mistakes of 5% or more in cumulative tumour dose occur in 3 to 4% of treatments shows that we have not yet solved the problem of delivering the prescribed dose to the target volume. In spite of my few points of criticism, this is an impressive report. Previous ones were aimed clearly at the physicist, but the refreshingly broader approach in ICRU 24 makes it essential reading for both physicists and clinicians actively involved in radiotherapy.

W. H. Sutherland.

1978, *British Journal of Radiology*, *51*, 5–10 JANUARY 1978

Pseudo-occlusion of the internal carotid artery

By P. Macpherson, F.R.C.R., D.T.C.D.

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(Received May, 1977 and in revised form June, 1977)

ABSTRACT

In a ten-year period, 31 cases of pseudo-occlusion of the internal carotid artery were seen; 42 carotid angiograms were available for analysis. On the first film of the series the contrast came to a tapered end in the cervical portion of the internal carotid artery in 16; extended to the carotid canal in 11; to the siphon in eight and to proximal intracranial vessels in seven. In 17 patients later films showed advance of the contrast. In four it did not get beyond the foramen lacerum; in eight it reached the siphon and in five the proximal intracranial vessels. Eight angiograms of patients with intracranial occlusion were examined and showed identical appearances.

Contrast opacified the middle menigeal artery in 29 of the 31 pseudo-occlusion cases. The circulation time was slow in 28. The circulation times through the middle menigeal artery were more or less identical with those in the superficial temporal arteries and unaffected by systolic blood pressure.

Twenty-three of the pseudo-occlusion cases were being ventilated and 25 had fixed dilated pupils. The commonest aetiological factors were trauma, haematoma due to ruptured aneurysm and primary tumour. In the occlusion group no case was being ventilated and only one had fixed dilated pupils. Course of action on finding the appearances of pseudo-occlusion is suggested.

The term pseudo-occlusion was proposed by Newton and Couch (1960) to describe an appearance first reported by Riishede and Ethelberg (1953) in five moribund patients with acutely raised intracranial pressure. Contrast does not usually progress beyond the carotid siphon and any filling of intracranial vessels that occurs is very slow and incomplete. Davies and Sutton (1967) reported five cases seen over the preceding 12 years to add the to 25 cases which they had culled from the literature. With the advent of EMI scanning, angiography is likely to be used less frequently in conditions associated with high intracranial pressure. It seemed appropriate, therefore, to review the angiograms performed in this Institute during the ten-year period 1966–75, as such numbers will not likely be available in the future. An additional reason is that there have been recommendations from some countries that this sign should be sought as confirmatory evidence of brain death.

METHODS

Contrast medium (10 ml) was injected by hand through a 17-gauge cannula into the common carotid artery. An automatic timing device gave 1.25 sec between each exposure. A non-screen film of the carotid bifurcation in the neck, taken as a routine, made it possible to verify that there was no technical reason for the appearances.

RESULTS

In the ten-year period under review there were 16 cases in which the contrast medium did not go

TABLE I

GROUP TO BE DISCUSSED

			Cases	Bilateral examinations		Unilat. exam.	Total car. angios for for analysis
				Bilat. pseudo-occl.	Unilat. pseudo-occl.		
Pseudo-occlusion	Contrast did not extend beyond siphon	Group I Arteries patent at autopsy	16	6	4	7*	23
		Group II no autopsy	6	2	2	2	8
	Contrast slightly beyond siphon	Group III Arteries patent at autopsy	9	2	4	3	11
		Total	31	10	10	12	42
Occlusion		Group IV	7	1	3	3	8

*Including a repeat of a bilateral examination.

TABLE II

COMPARISON OF THE CAROTID ANGIOGRAPHIC APPEARANCES IN THE PSEUDO-OCCLUSION AND OCCLUSION GROUPS

		Extent of contrast column on first film				Type of advance of contrast column			Extent of advance of contrast on fifth film		
		Tapered end in neck	Carotid canal	Siphon	Proximal intracranial vessels	Not advanced	On with a head	Layered	Carotid canal	Siphon	Intracranial branches
Pseudo-occlusion	Group I carotid angios 23	14	6	3	0	11	4	8	4	8	0
	Group II 8	2	3	3	0	8	0	0	0	0	0
	Group III 11	0	2	2	7	6	2	3	0	0	5
	Total 42	16	11	8	7	25	6	11	4	8	5
Occlusion	Group IV 8	4	2	2	0	3	0	5	1	3	1

beyond the carotid siphon and in whom subsequent post-mortem examination demonstrated patent arteries (Group I); six similar cases in whom no necropsy was done (Group II); nine in which the contrast extended slightly into the supraclinoid vessels and in whom the post mortem demonstrated patent arteries (Group III). In addition there were seven cases with radiological pseudo-occlusion but in whom the appearance was actually caused by thrombosis or embolus (Group IV).

The radiological features of each side of a bilateral angiogram have to be examined separately so that in certain tables it will appear that in Group I there were 23 carotid arteriograms for analysis; eight in group II; 11 in Group III and eight in Group IV. (Table I).

Carotid appearances (Table II)

On the first film of the series the contrast column came to a tapered end in the internal carotid artery in the neck in 16 of the 42 angiograms in the pseudo-occlusion groups (I–III), (Fig. 1). It extended to the carotid canal in 11; to the siphon in eight, and to the proximal intracranial vessels in the remaining seven. On the subsequent films there had been no progress of the contrast column in 25. In 11 the column had advanced in a layered fashion (Fig. 2). and in six by a head of contrast (Fig. 3). In four of the 17

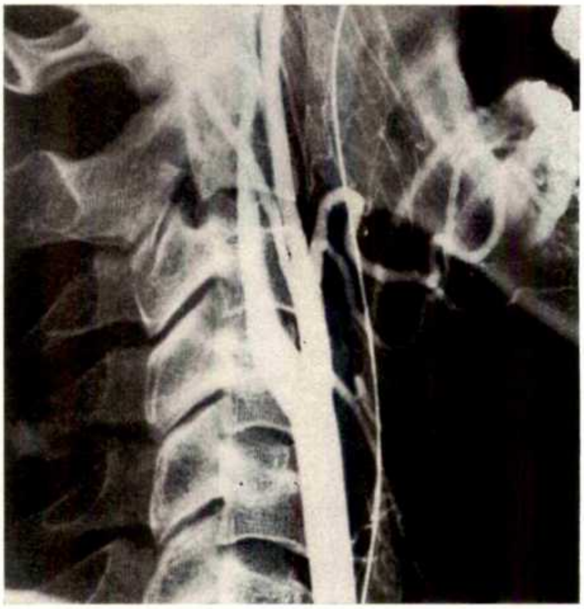
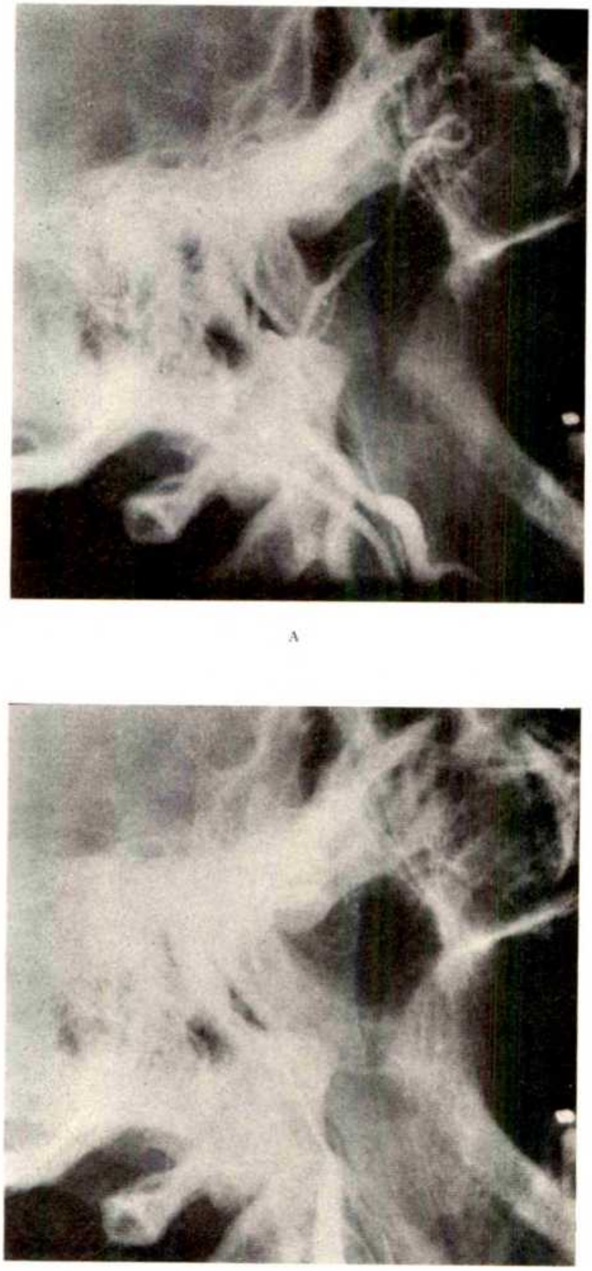


FIG. 1.

Pseudo-occlusion case. At the time of the first film of the series, the contrast in the internal carotid artery came to a tapered end in the neck.


A

B

FIG. 2.

Pseudo-occlusion case. (A) First film. (B) Film 5 sec later showed that the contrast column had advanced in a layered fashion.

angiograms where the contrast advanced it did not get beyond the foramen lacerum; in eight it reached the siphon and in five the proximal intracranial vessels. From the eight angiograms in Group IV (occlusion cases) it would seem that identical appearances may result from thrombosis or embolus. The contrast came to a tapered end in the internal carotid artery in the neck on the first film in four (Fig. 4); in two it reached the carotid canal and in two the siphon. Subsequent films showed no progress of the contrast column in three cases while in the other five the column had advanced in a layered fashion. In one of these it reached the carotid canal (Fig. 5); in three the siphon (Fig. 6) and in one extended slightly into proximal intracranial branches. In one case bilateral examination showed features identical with those seen in the pseudo-occlusion cases, but autopsy revealed bilateral emboli.

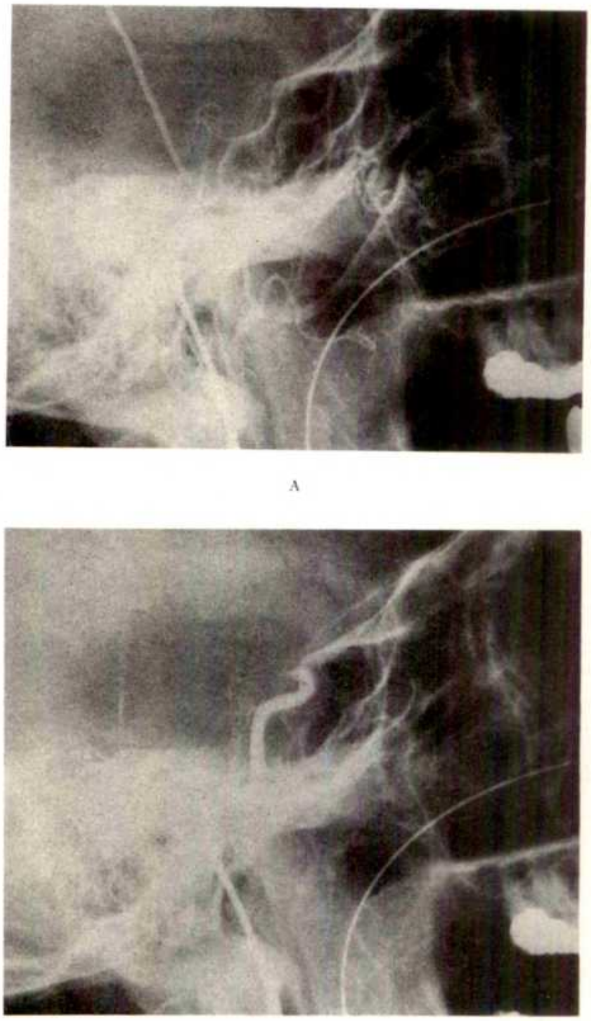

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FIG. 3.

Pseudo-occlusion case. (A) Third film of series. (B) $2\frac{1}{2}$ sec later showed advanced by a head of contrast.

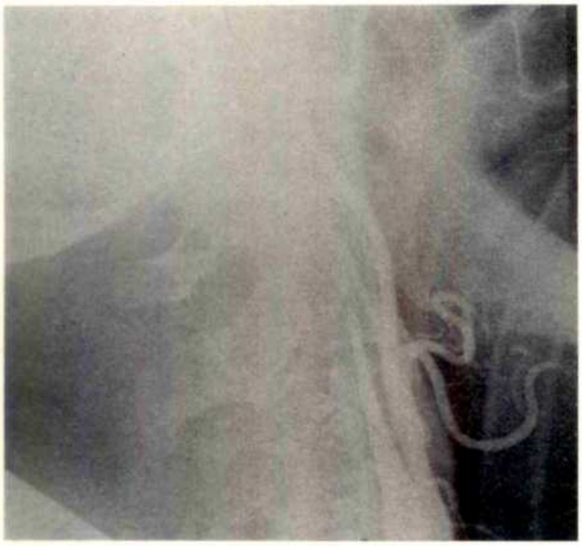

FIG. 4.
Occlusion case. At the time of the first film of the series, the contrast in the internal carotid artery came to a tapered end in the neck. (Compare Fig. 1.)

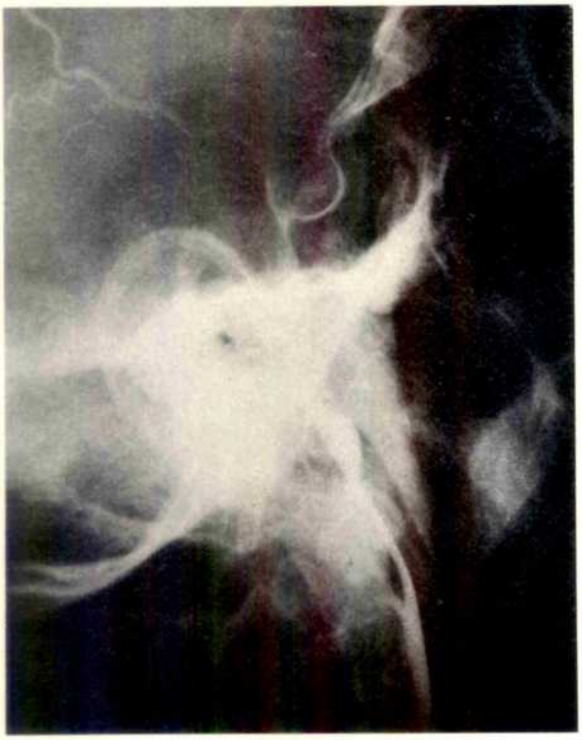

FIG. 5.
Occlusion case. Same case as Fig. 4. Five seconds later the contrast had reached the carotid canal.

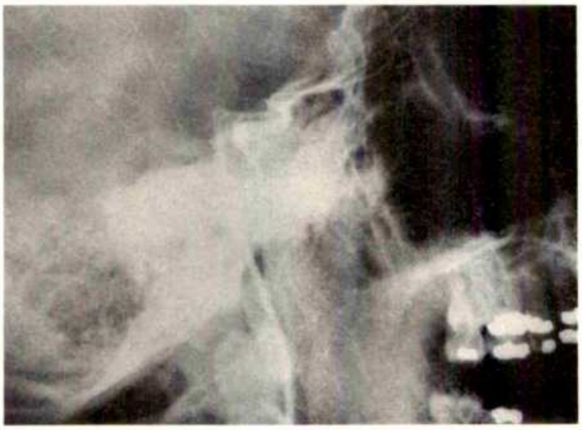

FIG. 6.
Occlusion case. The final film in a series showing that the contrast had reached the carotid siphon. (Compare Fig. 3B.)

Circulation through the middle meningeal artery

Contrast failed to enter the middle meningeal artery within the skull in only two of the 31 pseudo-occlusion cases. However using the criteria of Macpherson and Graham (1973), circulation through the middle meningeal arteries was markedly slow in 19; moderately in eight; slightly in one and normal in only one. Circulation was markedly slowed in four of the five occlusion cases in which estimation was possible.

Comparison of circulation times between the middle meningeal and superficial temporal arteries

In 23 of the 31 pseudo-occlusion cases the circulation rate in the superficial temporal artery was the same as that in the middle meningeal artery. In three cases the rate in the middle meningeal artery was slightly and in two moderately slower. In a further two the contrast did not get into the intracranial part of the middle meningeal artery. In the remaining case the rate in the superficial temporal artery was slightly slower. The rates were the same in four of the six occlusion cases in which comparison was possible, and slower in the superficial temporal in the remaining two.

Clinical state at time of angiogram

In 25 of the 31 pseudo-occlusion cases the pupils were fixed and dilated, one had reacting pupils and the state of the pupils had not been recorded in the remaining five. Twenty-three cases were being ventilated; three others had had periods of apnoea and a further case required to be kept on a ventilator after angiography. In the occlusion group one case had fixed dilated pupils and died from massive brain infarction with swelling. No case was being ventilated. The systolic blood pressure recording at the time of angiography was > 80 mm mercury in 24 of the 31 cases. In no case was there a recording below 60.

Aetiological factors (Table III)

The commonest intracranial lesions were traumatic in origin, haematoma due to ruptured berry aneurysm and primary tumour.

Association with raised intracranial pressure

Raised intracranial pressure was confirmed in all 25 cases in which post mortem examination was carried out.

DISCUSSION

Failure to demonstrate the intracranial vessels at carotid angiography may be technical but such appearances are unlikely to give rise to confusion. Experimental work by Mitchell *et al.* (1962) showed that when the intracranial pressure equalled the diastolic blood pressure, spontaneous respiration ceased and when it equalled the systolic blood pressure the intracranial vessels could no longer be filled under the standard conditions of injection, but that some filling could be achieved by forced injection.

Hugh and O'Malley (1975) stated that the appearance of pseudo-occlusion was quite different from the local stasis seen in patients with cerebro-vascular disease because it extended the full length of the vessel with a thickness depending on the degree of slowing.

In the present series the commonest radiological appearance was in fact a tapered stop in the internal carotid artery in the neck on the initial film without further progress of contrast. Other cases showed a build-up of contrast in dependent portions with a spill over into the next concavity. On a few occasions the contrast advanced with a "head". These changes are presumably related to the level of intracranial pressure and to gravity, though the force of injection might play a part. Glickman *et al.* (1972) used gravity-assisted arteriography in two cases of pseudo-occlusion. By putting the patient into the hanging head position, the intracranial vessels were below the level of the internal carotid arteries. A subsequent injection resulted in sufficient intracranial filling to be of diagnostic value.

In the present series there were five cases which showed no supraclinoid contrast on one side but

TABLE III

LESIONS ACCOUNTING FOR THE PSEUDO-OCCLUSION

Reviewed by	Cases	Head injury	S.A.H with haematoma	Primary haematoma	Angioma	Primary tumour	Metastasis	Meningitis	Abscess	Hepatic coma	Drug overdose cardiac arrest
Davies and Sutton, 1967	31	4	11	3	3	4	1	1	4	0	0
Berquist and Bergström, 1972*	28	8	8	3	1	4	0	0	0	1	0
Macpherson, 1977	31	11	12	0	0	5	1	1	0	0	1

*Done for confirmation of cerebral death.

slight outlining of proximal intracranial vessels on the other side. In the four of these which had post-mortem examinations, the contrast had failed to enter the supraclinoid vessels on the side of the space occupying lesion. There were two patients with calcification in the siphon and proximal middle cerebral artery. In both, the contrast extended into the middle cerebral artery to the end of the calcified section. This raises the possibility that the rigidity of the wall prevented the pressure effect on the artery.

The fact that the intracranial portion of the middle meningeal artery was outlined in all but two cases lends support to the belief that the extra and intradural pressures are not always equal.

Of the 31 cases reviewed by Davies and Sutton (1967), 18 required artificial ventilation and a further two had Cheyne Stokes respiration. In the present series an even greater proportion had respiratory difficulty. In the occlusion group (Group IV) none was being ventilated and only one had fixed dilated pupils. The clinical state therefore is important in the interpretation of the angiographic appearance.

As in the other series reviewed, the most common intracranial lesions were traumatic in origin, haematoma and primary tumour.

All 31 cases in the pseudo-occlusion groups (I–III) died so that it might be assumed that the appearances are synonymous with, or will be followed inevitably by, brain death. However, identical appearances were shown in the Group IV (thrombosis and embolus) cases described. If such an obstruction is beyond the origin of the ophthalmic artery, the escape of blood into this vessel will allow a little flow to continue in the internal carotid artery thus mimicking a pseudo-occlusion.

There is always the possibility that one is examining the patient during a plateau wave of intracranial pressure. There may, therefore, be a place for making an immediate burrhole with ventricular decompression followed by a further attempt to show a remediable lesion.

Suggested course of action on finding appearances of pseudo-occlusion

1. Immediately elevate the patient's head to drain contrast from the dependent loops, as pooling may be causing a complete obstruction to the blood flow.
2. Perform arteriography on the other side, because unilateral thrombosis and embolism can produce identical appearances.
3. Repeat arteriography (lateral and basal views) with the patient in the hanging head position, as the assistance of gravity may result in sufficient contrast entering the intracranial vessels to be of diagnostic value.
4. Consider from the history and clinical state whether immediate ventricular decompression is justified with a view to gaining time for a further diagnostic procedure, in the hope of finding a remediable lesion.
5. Scrutinize closely the external carotid branches for evidence of meningioma.

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Urinary excretion and patterns of protein binding of iodipamide (Biligrafin forte)

A comparison of the infusion technique with the single bolus injection in intravenous cholangiography

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ABSTRACT

It has been suggested that the bile ducts are seen better during intravenous cholangiography when the contrast medium is given by infusion rather than by injection in a single bolus. As an explanation, it has been proposed that a greater amount of contrast medium is bound to plasma proteins after infusion, resulting in a smaller quantity of contrast medium being excreted in the urine, so leaving a larger total for excretion by the liver.

In this study, the urinary excretion of ^{125}I labelled iodipamide methylglucamine (50% w/v Biligrafin forte) has been measured in 42 patients. The patients were divided into two groups. One group received a slow infusion of radioactive iodipamide over 45 minutes and the other an intravenous injection over five minutes. When a relatively high dose (0.6 mg/kg body weight) was used, no difference in urinary excretion was noted between these two groups; but with a lower dose (0.2 mg/kg body weight), slow infusion resulted in a reduced urinary excretion: however the total difference in contrast lost in the urine was too small to affect biliary concentration.

The patterns of protein binding of iodipamide have been examined in 12 of these patients. The results show that at the low dose a higher percentage of radioactive iodipamide is bound to protein in patients given contrast by infusion. There is clear evidence that the contrast binding capacity of plasma is limited so that with higher doses, much contrast remains unbound. At any given dose level, there is an inverse correlation between the proportion of contrast bound to protein and the urinary excretion. The factors affecting contrast binding in individual subjects are not clear.

Two reasons have been given for preferring the infusion technique in intravenous cholangiography. One is that side effects are reduced (Darnborough and Geffen, 1966; McNulty, 1968; Foy, 1968; Nolan and Gibson, 1970). The other is that there is said to be improved visualization of the bile ducts (Feldman and Keohane, 1966; McNulty, 1968; Payne, 1968; Painter, 1972), though this is not generally accepted.

As an explanation for the latter, it has been suggested (Cooperman *et al.*, 1968) that with the infusion technique, a greater amount of contrast is bound to plasma protein and that this results in a smaller quantity of contrast medium being excreted in the urine, and hence a larger quantity in the bile. To test this hypothesis the urinary excretion of iodipamide (50% w/v Biligrafin forte) labelled with ^{125}I sodium iodipamide has been compared, using the slow infusion technique and the bolus injection. We have also examined the patterns of contrast binding in the serum using the radioactive tracer dose technique in a small number of patients, and have compared the cholangiographic quality after different dosages and forms of administration.

METHODS

Forty-two adult patients between the ages of 29 and 75 years (22 males and 20 females) requiring intravenous cholangiography were investigated. The purpose of the investigation was explained to them and their consent obtained. Ethical committee approval was also obtained for the project. Patients were excluded from the study if they were under 21 or over 75 years, if there was any history of thyroid disease or if they were taking barbiturates, sulphonamides or sulphonyl urea drugs. Premenopausal women were not studied because we used a radioactive tracer dose technique for estimations on blood and urine samples. Serum bilirubin, plasma creatinine and plasma proteins were estimated and patients excluded from the study if the serum bilirubin was greater than 17 μmol/l, plasma creatinine greater than 130 μmol/l or if the plasma proteins showed any abnormality.

All patients received 50% w/v iodipamide methylglucamine (Biligrafin forte Schering Chemicals Ltd) to which had been added 5 μCi of ^{125}I sodium iodipamide obtained from Schering Chemicals Ltd. This solution will be referred to as radioactive iodipamide. The patients were divided by random selection into two groups. Group A received 0.6 ml/kg body weight of radioactive iodipamide in an injection given over five minutes, followed by 250 ml 0.9% saline over the next 40 minutes. Group B received 0.6 ml/kg body weight of radioactive iodipamide diluted in 250 ml 0.9% saline by intravenous infusion over 45 minutes.

A further series of tests using a lower dose was carried out on the following two groups. Group C received 0.2 ml/kg body weight of radioactive iodipamide in an injection given over five minutes, followed by 250 ml 0.9% saline over the next 40 minutes. Group D received 0.2 ml/kg body weight of radioactive iodipamide diluted in 250 ml 0.9% saline by intravenous infusion over 45 minutes.

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All patients were given a five-day course of potassium iodide (100 mg daily) to prevent uptake of the radioactive iodipamide by the thyroid gland. On the morning of the examination, a control film was taken and the subject then emptied his/her bladder. The subject then received either the intravenous infusion or a single bolus injection. Urine was collected for the first three hours and then for the subsequent 21 hours.

The urinary excretion of radioactive iodipamide was then estimated as a percentage of the administered dose by measuring the radioactivity in each urine sample and in an aliquot of the administered dose. A well scintillation counter was used.

The percentage of iodipamide bound to serum protein was estimated in three patients in each group. Each sample of serum was separated into two portions. In one portion serum, contained in Visking tubing, was dialysed against 0.9% saline w/v for 24 hours at ±4°C. The free ^{125}I contrast was thus dialysed out and the serum protein retained within the Visking tubing. The residual ^{125}I activity within the Visking tubing was then counted. This latter activity was compared with the total contrast radioactivity in the other portion of serum and the percentage of contrast bound to the protein was then calculated. The results are expressed as protein binding of iodipamide.

Radiographs including three layer tomography were exposed 45 minutes after the beginning of injection/infusion with further tomographs as required to show the duct adequately and with late films, if needed, to show the gall-bladder. The radiographic quality of 36 examinations was assessed by grading them as good, adequate and poor. In the "good" examinations, the concentration in the ducts was sufficient to show hepatic ducts clearly and the bile duct was sharply defined. In the "adequate" examinations the bile duct was visible but the outline was less clear and hepatic ducts were not well shown. "Poor" studies were those in which the ducts were not seen sufficiently well for diagnostic purposes.

Results

50% radioactive iodipamide 0.6 ml/kg body weight. Groups A and B

The results of tests in 12 patients who received a bolus injection (Group A) and those who received a

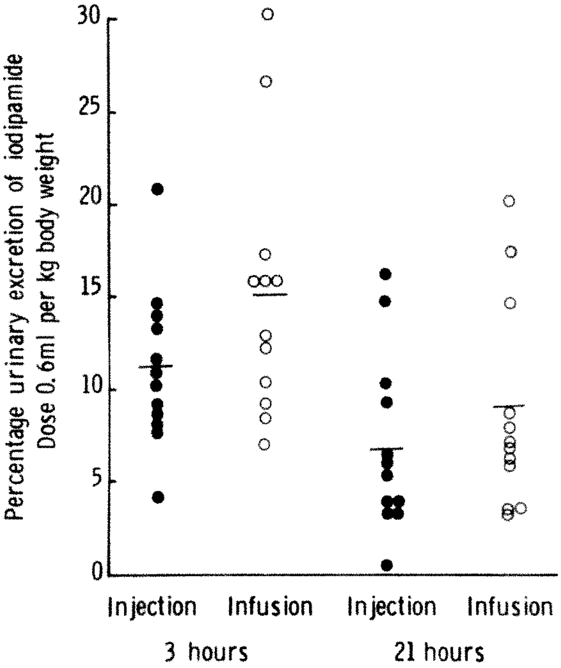

Fig. 1.

Urinary excretion of radioactive iodipamide 0.6 ml per kg body weight—expressed as a percentage of the total dose administered. The mean values for each group are shown.

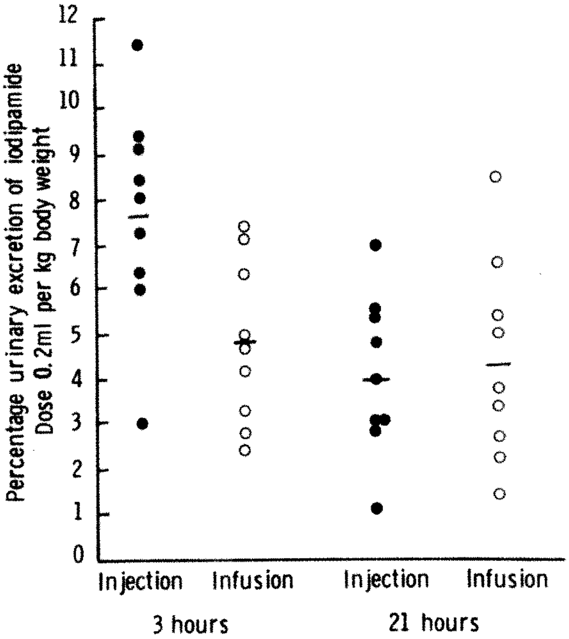

Fig. 2.

Urinary excretion of radioactive iodipamide 0.2 ml per kg body weight—expressed as a percentage of the total administered dose. The mean values for each group are shown.

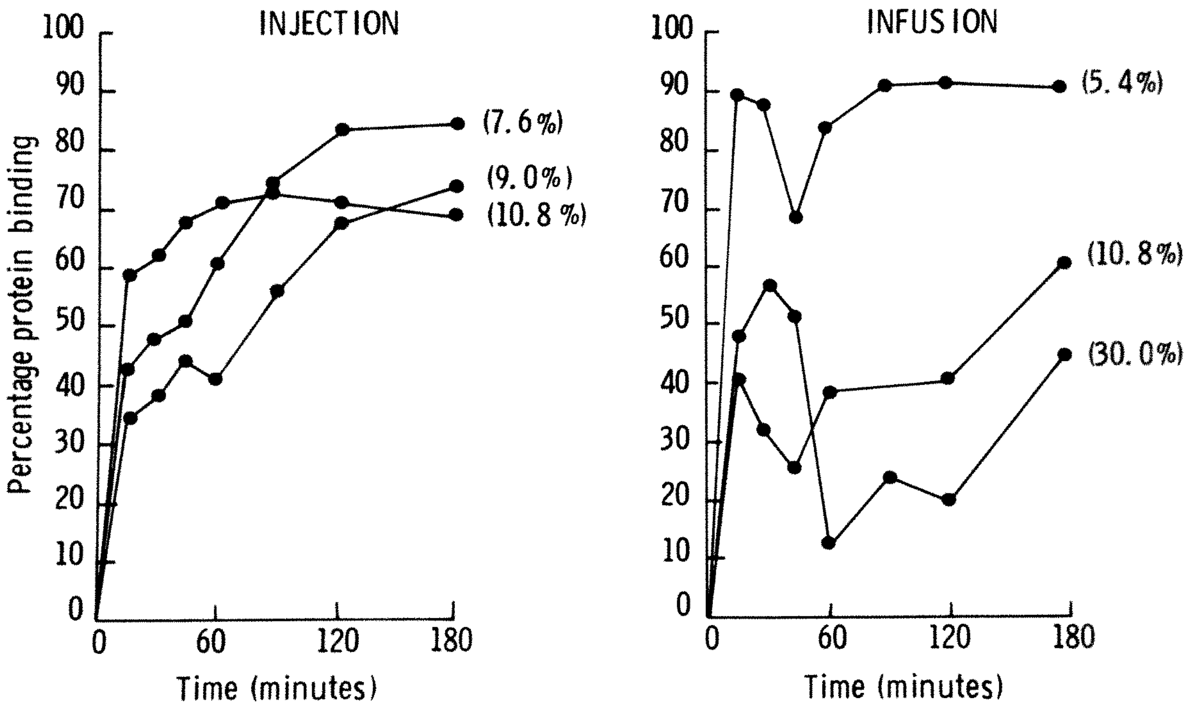

FIG. 3.

Percentage of radioactive iodipamide bound to serum protein using the dose 0.6 ml per kg body weight. Percentage urinary excretion of iodipamide during first three hours shown in brackets.

slow intravenous infusion (Group B) are shown in Fig. 1. The percentage of radioactive iodipamide excreted in the urine is plotted on the ordinate. During the first three hours the mean percentage excretion for the injection group was 11% (S.E. ±1.2) and for the infusion group was 15.1% (S.E. ±2.0). The difference between the two means is not significant. The mean percentage urinary excretion over the subsequent 21 hours for the injection group was 7.1% (S.E. ±1.3) and for the infusion group was 9.0% (S.E. ±1.6). The difference between these two means is again not significant.

50% radioactive iodipamide 0.2 ml/kg body weight. Groups C and D

The results of nine patients who received a single bolus injection (Group C) and nine who received a slow infusion (Group D) are shown in Fig. 2. During the first three hours the mean percentage urinary excretion of radioactive iodipamide in the injection group is 7.7% (S.E. ±0.8) and in the infusion group 4.8% (S.E. ±0.6). The difference between these two means is significant (p 0.01, one tailed test). There is no significant difference between the means for the subsequent 21 hours.

Figures 3 and 4 show the patterns of protein binding during the first three hours after commencing administration of contrast. After injection of 0.6 ml/kg iodipamide much of the contrast is at first unbound, the percentage rising later when the plasma level will be falling. Infusion gives rather different patterns of percentage binding but total binding during this period is no greater than after injection. Following the lower dose of 0.2 ml/kg the protein binding patterns are more consistent. With injection the percentage binding rises steadily towards 100%. During infusion almost 100% binding is reached quite early and there is then a temporary drop in percentage binding, indicating that during this period there is an excess of contrast over the available binding sites.

Table I sets out the results of the assessment of radiographic quality in the cholangiograms obtained from the four groups of patients (A, B, C and D).

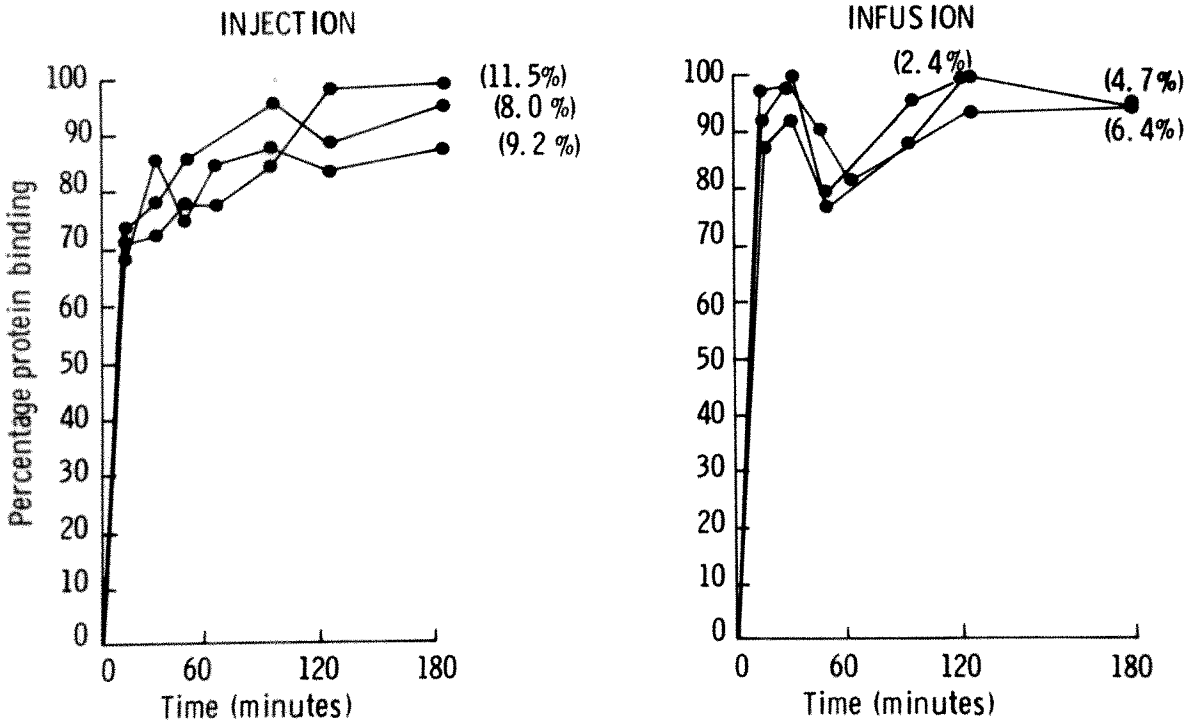

Fig. 4.

Percentage of radioactive iodipamide bound to serum protein using the dose 0.2 ml per kg body weight. Percentage urinary excretion of iodipamide during first three hours shown in brackets.

TABLE I

Assessment of radiographic quality in Groups A, B, C and D

	High dose (22 patients)				Low dose (16 patients)			
	Injection A	Infusion B	Total	%	Injection C	Infusion D	Total	%
No. Examinations	10	12	22	100%	9	7	16	100%
Scores: Good	8	8	16	73%	7	5	12	75%
Adequate	2	3	5	23%	2	2	4	25%
Poor	—	1	1	4%	—	—	—	—

Twenty-two patients received the high dose (Groups A and B), and 16 the low dose (Groups C and D). Although the total number of examinations assessed for radiographic quality is small, there is no significant difference in the scores (good, adequate and poor) when the high dose is compared with the low dose and the injection compared with infusion.

Discussion

Biliary contrast media are known to become bound to protein in the plasma though it is not now believed that this is a necessary preliminary to hepatic excretion (Knoefel, 1971; Song *et al.*, 1976). Animal work by Lasser *et al.* (1962), Fischer (1966) and Feldman and Keohane (1966) has been taken by Cooperman *et al.* (1968) to suggest that slow infusion might act differently from bolus injection by allowing more time for protein binding of contrast, so reducing the amount available for glomerular filtration. It was further suggested that hepatic excretion might be increased by this means. It is clear that if the urinary contrast output were similar after infusion and after bolus injection this hypothesis would be invalidated and this was the basis for our study. We chose a three hour period for our initial collection because this covers the time during which the examination is usually performed and when differences in excretion might affect the radiographs.

Clearly, it would be preferable to undertake direct estimation of biliary contrast medium in man as has been done in the experimental animals. There are, however, a number of difficulties in making extensive studies of this sort. With present techniques it can only be done after insertion of a T-tube and it is then essential to maintain an intact enterchepatic circulation to avoid misleading results (Whitney and Campbell, 1972). Animal studies indicate that a period of at least two weeks is required after insertion of a T-tube before dependable results are obtained (Dowling *et al.*, 1970). Furthermore, cholangiographic contrast media carry a small but definite risk which makes it hard to justify their use for experimental purposes. For these reasons we felt that, with all its drawbacks, the study of biliary contrast handling by measuring urinary spill-over might give some information of interest.

Urinary contrast loss

In the first series of tests a dose of 0.6 ml/kg body weight of radioactive iodipamide was used. This dose was found to be the optimum in dog experiments by Fischer (1965). For a 70 kg adult this is a dose of approximately 40 ml, a volume commonly used in many radiological departments when iodipamide methyglucamine (Biligrafin forte) is given. With this dose there is no difference in the proportion excreted by the kidneys either in the first three hours or in the subsequent 21 hours. Using the smaller dose of 0.2 ml/kg body weight (14 ml for a 70 kg man) there is a significantly higher urinary excretion of radioactive iodipamide when this is given by a single bolus injection. However, the difference is only 4% of the total dose given and this could not materially affect the biliary concentration of contrast. Any difference which the infusion method may produce in the hepatic handling of contrast is not, we believe, secondary to differences in urine loss.

Whitney and Bell (1976), working with rhesus monkeys, have shown that a two-hour infusion of contrast leads to a prolongation of the peak concentration of contrast. Thus the advantage of the infusion probably lies, not only in a reduction of side-effects but in a lengthening of the optimal period during which opacification will occur.

Serum protein binding

The patterns of protein binding of contrast in the four groups show interesting differences. They indicate that the contrast-binding capacity of plasma protein is limited. Thus with the higher dose given by bolus injection there is initially a considerable excess of plasma iodipamide in relation to the available binding sites. The continuing excretion of contrast lowers the total level so that proportionately more becomes bound to protein. Even with infusion, using the higher dose there is a considerable surplus of contrast unbound to protein. At the lower dose level the surplus of contrast over the binding capacity of plasma is less and a higher proportion becomes bound to protein soon after injection. Towards the end of the infusion of contrast with both high and low doses there is a drop in the percentage-binding, indicating a temporary excess of contrast over the available binding sites. Patients appear to vary in the contrast binding capacity of their plasma but we could find no relationship between urinary contrast loss and the plasma protein level. It might be expected that urinary contrast loss would be greatest when the percentage protein binding was least and with one exception the figures support this.

Cholangiography

We have not shown any difference in cholangiographic quality between high and low doses. It is possible that our assessment did not detect differences in contrast density which would have been chemically demonstrable, but there are reasons for believing that current doses are unnecessarily high. Hepatic excretion of contrast is subject to a transport maximum (TM) (Preisig and Hoenig, 1973) and doses in excess of the TM will either be excreted in the urine or undergo delay in hepatic excretion. The TM for iodipamide is probably similar to that for ioglycamide which was estimated by Fuchs and Preisig (1975) at 19 to 23 mg/min. Their subjects were studied only a week after cholecystectomy, and may have had disturbed liver function; nevertheless the optimal TM is unlikely to exceed 30 to 35 mg/min. Even the lower dose level which we have employed was well in excess of the likely TM for iodipamide and assuming that TM is the main factor affecting biliary contrast concentration, our findings are not surprising. Other workers (Sinclair, 1972; Ansell and Faux, 1973) have shown that satisfactory cholangiograms can be obtained with doses below 20 ml iodipamide and our series, although small, reinforces their findings.

Conclusions

Currently employed dose levels of biliary contrast exceed the plasma's capacity to bind contrast and lead to appreciable urinary loss. Lower dose levels provide equally good cholangiograms with less urinary excretion. The drip infusion method provides a higher percentage binding at low dose levels. It is unlikely that this is significant in relation to biliary excretion.

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Book review

Coronary Angiography and Angina Pectoris. Edited by P. R. Lichtlen, pp. xx+384, Illust., 1976 (Stuttgart, George Thieme), DM.68.

This book is a compilation of the papers presented at the Symposium of the European Society of Cardiology on the subject of Coronary Angiography and Angina Pectoris, held in Hanover in March 1975. Three-quarters of the book is devoted to coronary angiography and one-quarter to a workshop on "Collateral formation and treatment of angina pectoris". The subjects covered include X-ray techniques; the relationship of angiographic findings to various clinical problems *e.g.* variant angina, unstable angina, prognosis based on angiographic findings; ventriculographic aspects of coronary artery disease; and angiography after surgery.

The contributors came from all over Europe and North America and contained many of the foremost workers in these fields. Nearly 70 papers were delivered; most of them presented here in detail, with good illustrations. The salient remarks from the discussions that followed each paper are included.

This is a well produced record that will be of great interest to those with a specialist interest in coronary artery disease.

P. Armstrong.

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A simple spectrophotometric method for measuring biliary ioglycamide (Biligram) concentration*

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ABSTRACT

An extremely simple spectrophotometric method for measuring biliary ioglycamide (meglumine ioglycamate) concentration is described. It was validated by a radioactive technique.

Little information is available as to what is the optimal rate for administering ioglycamide (Biligram—Schering Chemicals Ltd.) to the patient when performing an intravenous cholangiogram. In an attempt to answer this question we have measured the concentration of ioglycamide appearing in the bile of a series of patients with *T*-tube *in situ* who were given the contrast material at a number of different infusion rates. The simple spectrophotometric method used in these studies to measure the biliary concentration of ioglycamide is described and validated in this paper.

PRINCIPLE OF THE METHOD

Ioglycamide (meglumine ioglycamate) is strongly absorbent in the ultra-violet region with a maximum absorbance at 237 nm (Fig. 1). Fleck *et al.* (1974) have recently described a simple spectrophotometric method for determining the plasma concentration of ioglycamide. This method entails diluting the plasma samples 100 times with isotonic saline and measuring the absorbance at a wavelength of 245 nm. This wavelength was selected because it was found that the ratio of absorbance of contrast medium to that of plasma constituents, particularly albumin, is maximum at 245 nm (Medzihradsky *et al.*, 1975).

The concentration of ioglycamide achieved in bile is approximately ten to fifteen times that found in the plasma (Fuchs and Preisig, 1975). If a spectrophotometric method similar to the plasma method of Fleck *et al.* (1974) were to be used on bile samples one would predict that a dilution factor of about 1500 times would be required. Human *T*-tube bile samples were diluted 1500 times with isotonic saline and spectra obtained using an ultraviolet recording spectrophotometer (Unicam SP800). Very little absorbance was found in the 230—280 nm wavelength region (Fig. 1), presumably reflecting the low protein content of human bile (Thurborn, 1962). Figure 1 also shows the ultraviolet wavelength scan of human *T*-tube bile taken from a patient one hour after commencing an intravenous infusion of ioglycamide. It can be seen that ioglycamide is excreted into bile

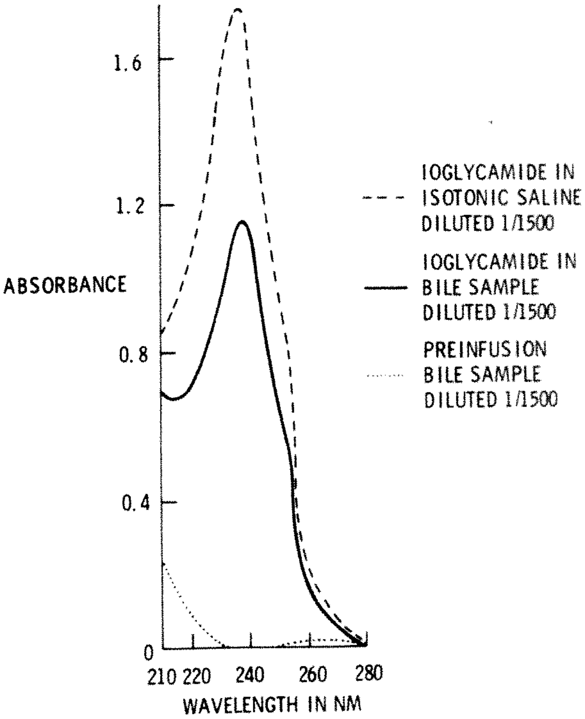

FIG. 1.

Ultraviolet absorption spectrum of ioglycamide diluted in isotonic saline and of human *T*-tube bile samples before and during an intravenous infusion of ioglycamide unchanged and that 237 nm would be the most suitable wavelength for measuring ioglycamide concentration in bile.

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*This work had received the approval of the St. Bartholomew's Hospital Ethical Committee and the informed consent of the patients was obtained before the investigations were performed.

†Present address: University Department of Therapeutics, City Hospital, Hucknell Road, Nottingham. Research carried out while holder of the Mackenzie Mackinnon Streatfield Research Fellowship.

MATERIALS AND METHODS

Intravenous infusion and bile sampling

The biliary excretion of ioglycamide was measured in two patients (A.T. and I.L.) who were operated on for gall stones and had a *T*-tube *in situ*. The ioglycamide solution was made up by adding 21 g of ioglycamide (2×30 ml ampoules of 35% Biligram—Schering Chemicals Ltd.) to 460 ml of normal saline and labelled with 20 μCi ^{125}I ioglycamide. The isotopically labelled stock solution infused thus contained 42 mg ioglycamide/ml. The ioglycamide was infused at a rate of 2 mg/kg body weight/min for 120 mins. The rate of administration was controlled using an Ivac 531 infusion pump (Ivac Corporation, Harrow, Middlesex). At the end of the intravenous infusion 10 ml of the remaining radioactively labelled ioglycamide was removed from the drip bottle and stored prior to radio-active counting.

Twelve consecutive ten-minute bile samples were obtained from both patients during the ioglycamide infusion. The concentration of ioglycamide in the 24 bile samples was then estimated by both the spectrophotometric and radioactive methods (to be described below). The results obtained by the two methods were then compared.

Spectrophotometric method

Stock solutions of ioglycamide in isotonic saline were made up to include a range of concentrations from 6 to 41 mg per ml. These stock solutions were then diluted by a factor of 1500 times with isotonic saline. The optical densities of the solutions were then read off the SP800 spectrophotometer at a wavelength of 237 nm using 0.9% of sodium chloride solution as a blank. The calibration curve obtained is shown in Fig. 2.

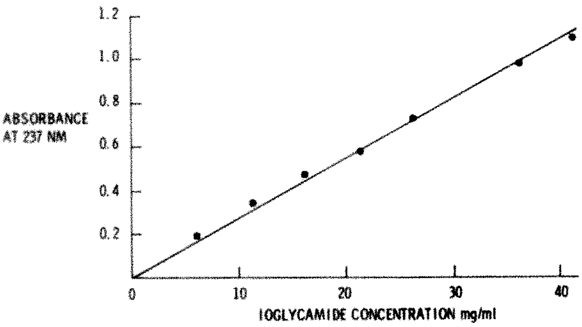

FIG. 2.

Calibration curve—ioglycamide in normal saline read at 237 nm.

The patient's bile was also diluted by a factor of 1500 times with isotonic saline before reading off the spectrophotometer as follows: 0.2 ml of each bile sample was diluted with 5.8 ml of 0.9% sodium chloride solution and mixed thoroughly. 0.1 ml of this diluted sample was then further diluted with 4.9 ml of 0.9% sodium chloride solution and thoroughly mixed before reading off the spectrophotometer at a wavelength of 237 nm (again using 0.9% sodium chloride solution as a blank). The concentrations of ioglycamide in each of the bile samples was then read off the standard curve after deduction of the absorbance for the 1 in 1500 diluted 'baseline" bile sample.

Radioactive method (Whitney and Bell, 1972)

The radioactivity of the patients' bile samples and their corresponding stock solutions were measured using a well-type scintillation counter (I.C.N. Gamma set 500). The concentration of ioglycamide in each sample was calculated by dividing the "activity" in the bile specimen by the "activity" of the corresponding stock solution and multiplying by a factor of 42 (the known concentration of ioglycamide in mg/ml in the stock solution infused).

RESULTS

The spectrophotometric method and the isotope method for measuring biliary ioglycamide concentration gave very similar results. The concentration

TABLE I

PATIENT A.T.—CONCENTRATION OF IOGLYCAMIDE IN HUMAN BILE (MG/ML)—A COMPARISON OF THE RESULTS OBTAINED USING (A) THE RADIOACTIVE AND (B) THE SPECTROPHOTOMETRIC METHOD. TIME IN MIN REFERS TO THE TIME FROM THE START OF THE TWO-HOUR INTRAVENOUS INFUSION OF IOGLYCAMIDE (2 MG PER KG BODY WEIGHT PER MIN). CORRELATION COEFFICIENT FOR THE TWO METHODS 0.964

Concentration of ioglycamide		
Time in minutes	Radioactive	Spectrophotometric
10	0	0
20	2.0	1.6
30	4.6	3.7
40	7.8	7.1
50	6.3	7.2
60	5.6	6.4
70	8.1	6.7
80	8.0	7.8
90	10.0	8.2
100	12.8	12.6
110	9.7	9.3
120	7.7	9.1

TABLE II

PATIENT I.L.—CONCENTRATION OF IOGLYCAMIDE IN HUMAN BILE (MG/ML)—A COMPARISON OF THE RESULTS OBTAINED USING (A) THE RADIOACTIVE AND (B) THE SPECTROPHOTOMETRIC METHOD. TIME IN MIN REFERS TO THE TIME FROM THE START OF THE TWO-HOUR INTRAVENOUS INFUSION OF IOGLYCAMIDE (2 MG PER KG BODY WEIGHT PER MIN). CORRELATION COEFFICIENT FOR THE TWO METHODS 0.989.

	Concentration of ioglycamide	
Time in minutes	Radioactive	Spectrophotometric
10	0.2	1.1
20	5.0	5.9
30	14.9	15.7
40	18.7	16.3
50	20.4	19.8
60	20.9	21.0
70	21.8	22.5
80	21.9	23.0
90	22.6	23.4
100	23.5	24.5
110	23.2	24.5
120	23.7	25.8

of ioglycamide in the bile of the two patients A.T. and I.L. as estimated by the two methods is shown in Tables I and II.

DISCUSSION

The measurement of the concentration of various contrast media in bile has usually been based on estimating their iodine content. These methods include fluorescent excitation analysis (Moss *et al.*, 1972), dichromatography (Edholm and Jacobson, 1959), radioactive iodine (Fischer, 1965; Whitney and Bell, 1972; Loeb *et al.*, 1975; Fuchs and Preisig, 1975; Cooke and Mudge, 1975) or the more tedious and time-consuming direct chemical analysis of iodine content (Bang and George, 1951; Zak and Boyle, 1952). A recent paper which describes the biliary excretion of both calcium ipodate and iodipamide in the dog has employed a spectrophotometric method at a wavelength of 239 nm, but details of the exact method used are not given (Benness *et al.*, 1975).

The spectrophotometric method described in this paper has the advantage of being simple, quick and does not require the use of elaborate equipment or radio-isotopes. This method could easily be modified to measure the biliary concentrations of other biliary contrast agents such as iodipamide and iotroxamide.

ACKNOWLEDGMENTS

This work was in part supported by a grant from Schering AG who also supplied the labelled ioglycamide. Financial support from the Joint Research Board of St. Bartholomew's Hospital and the Duchess Peel Memorial Fund is also gratefully acknowledged. One of us (CDB) was in receipt of a grant from the Mackenzie Mackinnon Streatfield Research Fellowship. The authors are grateful to Dr. A. M. Dawson for his help and encouragement.

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A simple coding system for a diagnostic X-ray department

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Abstract

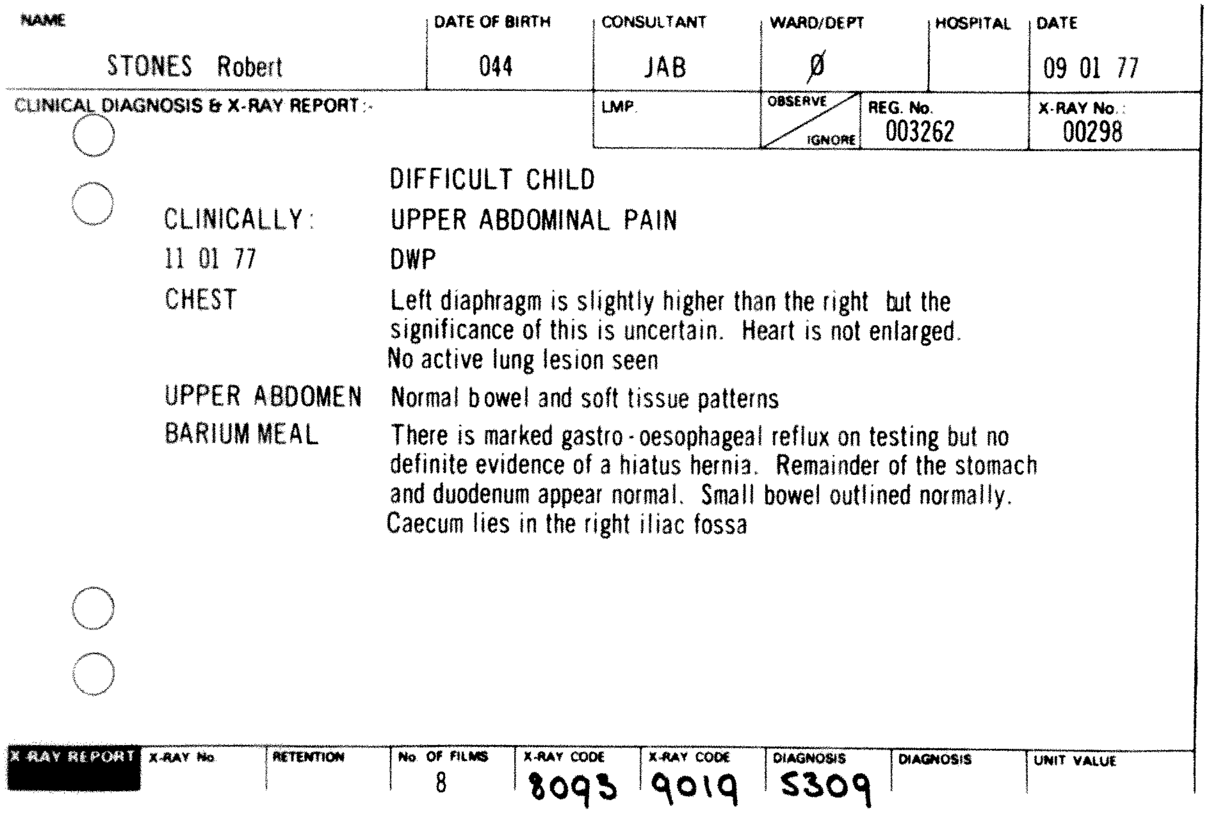
A simple coding system that codes the work done and diagnoses is described. It is economical and designed to withstand changes in staff.

As one of the most expensive departments of a hospital, using techniques potentially dangerous to the patient, the need for a continuous quantitative and qualitative review of the work of the X-ray department is self-evident. The need becomes even more pressing with the imminent advent of departmental budgeting.

A qualitative assessment of the work with information on the investigations carried out, the diagnosis made and their follow up is not a feature of any review system in regular use in the United Kingdom, except at the Birmingham Children's Hospital. Yet this would appear to be an essential prerequisite if long term information on the value of radiology in specific conditions is ever to be determined. A radiological coding system should, therefore, be able to carry out the following.

1. Retrieve cases of specific conditions.
2. Retrieve cases with specific radiological and clinical signs.
3. Provide managerial data for the X-ray department.

The need for such a system has been generally accepted, at least in teaching hospitals. So far, attempts to start and maintain an index system that codes all the examinations carried out have become bogged down by the sheer complexity of the radiological codes available, and therefore the great



NAME	DATE OF BIRTH	CONSULTANT	WARD/DEPT	HOSPITAL	DATE
STONES Robert	044	JAB	0		09 01 77

CLINICAL DIAGNOSIS & X-RAY REPORT:-	LMP	OBSERVE / IGNORE	REG. No.	X-RAY No.:
			003262	00298

	DIFFICULT CHILD
CLINICALLY:	UPPER ABDOMINAL PAIN
11 01 77	DWP
CHEST	Left diaphragm is slightly higher than the right but the significance of this is uncertain. Heart is not enlarged. No active lung lesion seen
UPPER ABDOMEN	Normal bowel and soft tissue patterns
BARIUM MEAL	There is marked gastro-oesophageal reflux on testing but no definite evidence of a hiatus hernia. Remainder of the stomach and duodenum appear normal. Small bowel outlined normally. Caecum lies in the right iliac fossa

X-RAY REPORT	X-RAY No	RETENTION	No OF FILMS	X-RAY CODE	X-RAY CODE	DIAGNOSIS	DIAGNOSIS	UNIT VALUE
			8	8093	9019	5309		

Fig. 1.
Report form with typical report.

amount of time, expertise and expense needed for their use, both in coding and recalling cases.

The criteria for a successful coding system therefore are: (1) it must not disturb the routine of the department; (2) it must be usable by changing population of radiologists and secretaries; (3) simple coding is needed suitable for non-medical coding clerk; (4) the system must be longlasting over the years; (5) it should be inexpensive.

THE SYSTEM

With these factors in mind, the following system has been devised in conjunction with the statistical section of the Trent Regional Health Authority, and put into use in the X-ray department of the Sheffield Children's Hospital. This department deals with children only and there are approximately 22000 attendances per year. Only minor modifications were needed to the report card. Figure 1 shows the format in use. Four copies of the report are obtained by using NCR paper. One of these copies is used for coding.

The card is filled in as follows:

Name	Both family name and first name are now coded. Initially only the family name was used but this made retrieval difficult.
Age	This is reported by the radiologist in months.
Consultant	This is the referring clinician and is inserted by the secretary.
Ward Registration number Date Film number	Put in by the secretary.
Retention	Never used.
Number of films	Dictated by the radiologist.

X-ray code (two boxes). This deals with the radiographic work load and the code for this was extracted from DHSS memorandum "Assessment of Radiographic Work Load in Diagnostic X-ray Departments of Hospitals and Clinics", July 1973. These boxes are filled in by the coding clerk from information extracted from the radiologist's report.

Parts of the codes are illustrated in Figs. 2 and 3. A code for uncooperative patients (the blind, deaf, children under six, mentally handicapped) is included. Four figures are put into each coding box.

X-RAY CODING SYSTEM (PART X-RAYED)

80	CHEST
81	CHEST - PA
82	CHEST - LATERAL
83	MANUBRIO STERNAL JOINT
84	RIBS
85	STERNOCLAVICULAR JOINT
86	STERNUM
87	THORACIC INLET
89	CHEST - SPECIAL VIEWS, DIAPHRAGM
90	ABDOMEN - URINARY TRACT - SUPINE - ERECT
93	UNCO-OPERATIVE PATIENT
95	SKELTAL SURVEY
98	FILLER-IN CODE
99	X-RAY, SITE NOT KNOWN

FIG. 2.

Section of list used to code part X-rayed. This provides the first two digits in the box marked X-ray code.

X-RAY CODING SYSTEM (INVESTIGATIONS)

00	NO INVESTIGATIONS
01	ANGIOGRAPHY
02	ANGIOGRAM - CAROTID
03	- VERTEBRAL
04	- CAROTID & VERTEBRAL
05	- COELIAC
06	- SUPERIOR MESENTERIC
07	- INFERIOR MESENTERIC
08	- AORTOGRAM - THORACIC
09	- AORTOGRAM - LUMBAR
10	- AORTOGRAM - TRANSLUMBAR
11	- FEMORAL
12	- BRACHIAL
13	- SUBCLAVIAN
14	PULMONARY ANGIOGRAM
15	RENAL ARTERIOGRAM - INFERIOR VENA CAVAGRAM
16	ARTHROGRAM
17	CONTRAST ENEMA - BARIUM
18	CONTRAST ENEMA WITH WATER SOLUBLE MEDIUM (GASTROGRAPHIN ENEMA HYPAQUE ENEMA)
19	BARIUM MEAL - BARIUM MEAL AND SWALLOW
20	BARIUM SWALLOW - CONTRAST STUDIES OF THE OESOPHAGUS
21	BARIUM MEAL AND FOLLOW THROUGH + GASTROGRAPHIN AND FOLLOW THROUGH
22	BARIUM SMALL BOWEL MEAL + SMALL BOWEL ENEMA

P 25,837

FIG. 3.

Section of list used to code investigation carried out. This provides the second two digits in the boxes marked X-ray code.

The first two digits indicate the part X-rayed by the radiographer. The second two indicate the type of radiological investigation, usually involving a radiologist, carried out. A code for portable or ward examinations is included. Should the number of investigations exceed the capacity of the boxes on one card (*e.g.*, a patient has a chest X-ray, barium meal and an IVP), the coding clerk will make out an extra card.

Diagnosis

Each patient is allowed to have two diagnoses per report card. They are dictated by the radiologist and can change during the progress of the patient's illness so that the final diagnosis coded for a particular patient can be corrected. The diagnoses are coded by the coding clerk using the "International Classification of Diseases" (WHO, 1967, 1969). A third box for diagnosis would be useful and we are planning to incorporate this soon. Batches of reports are collected twice a week and after coding are sent to the statistical section of the Trent Regional Hospital Authority where the information is transferred to punch cards.

Cost

The cost of coding 400 to 500 examinations per week is one part-time (eight hours/week) coding clerk (at approximately £500/year), plus the capacity to punch the cards (approximately £350/year).

Acceptability of the System

The system has not affected the radiographic staff at all. The radiologists have had to modify their reports slightly in that they have to quote the patient's age in months (good training for the 12× table!), give the number of films and the diagnosis. All X rays coming from casualty have been assumed to be trauma cases unless otherwise stated. The radiologist also indicates whether the patient merits "uncooperative" points and whether the examination was performed outside the X-ray department. The latter information is checked by the typist. The radiologist's work load has not increased significantly, and a changing population of senior registrars has coped well. The secretary's work has increased in that she has to fill in more boxes and produce an extra copy of the report. Use of NCR paper has greatly simplified this process. The part-time coding clerk is coping well with the case load of about 400 to 500 reports a week averaged over the year.

Use of the System

The system in its present form has only been functioning for 18 months. Before this the first names of the patients had not been coded and retrieval of the films and case notes was virtually impossible. There has not been time therefore to build up a big store of clinical diagnoses; however, retrieval of the names of patients suffering from inflammatory bowel disease and from hiatus hernia showed that the system was working satisfactorily. The names and registration numbers of all hip X rays from casualty during the last year have been obtained for the casualty officer. She is at present conducting an investigation into fractures in childhood and is being provided with the names and numbers of patients aged 0–2 and 3–5 years. The system has been used to assess the daily work load of the department coming from casualty and the percentage of positive findings. For instance, between May 1975 and May 1976, 1722 skull examinations were performed and of these 52 (3%) showed fractures.

A researcher into bone developments has been supplied with the names of patients under five years who have had their hands X-rayed.

A monthly report on the number of X-ray examinations carried out with their points value was provided for the first year. This led to a more detailed use of the work register kept by the desk clerk, with the result that the number of work points credited to the department increased. This is in keeping with the findings of Davies *et al.*, 1974. This monthly report has now been discontinued since it could not be provided in time for the monthly returns which have to be ready by the first Tuesday of the following month. Obviously, an increase in staff would speed up the system.

Should the concept of internal departmental budgeting and of charging the cost of radiological procedures to the various referring services ever be accepted, this system is capable of providing the information that will be needed.

Discussion

The system is simple and flexible. It does not provide a coded description of the X ray film itself, although many of the radiological appearances can be deduced from the clinical diagnosis, *e.g.* the presence of pleural effusions, metastases in the chest, strictures in the bowel.

Owing to the simplicity and unobtrusiveness of the system it has been accepted by the staff and has continued to function smoothly despite regular changes in secretaries and radiologists.

The simple diagnostic coding system will supply the radiologist researching into a clinical condition with a broad list of patients of whom only some will have the particular anomaly in which he is interested. For instance, if he is interested in ASD with anomalous veins he may well have to look through all cases of ASD to make sure he finds all those with anomalous pulmonary veins. However, this is not necessarily a severe drawback since no coding system is likely to code all the information the researcher needs, so that he will inevitably finish up by going through all the case notes anyway.

It should be possible to extend the system easily to other hospitals without disruption of their work.

The system provides a satisfactory record of the work carried out in a diagnostic X-ray department, and will make it possible to follow the course of a disease over many years.

All information coded is treated as strictly confidential. The report cards used for coding are destroyed after use and retrieval of information is only allowed following authorization by named personnel.

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This work has been carried out in co-operation with the Trent Regional Health Authority without whose support and encouragement it would have been impossible. Thanks are due to Mr. G. Porter, Mrs. P. Lyons, Dr. B. T. Williams and Mr. K. Trout and Mrs. E. Fitter who put the diagnostic code into practice, and to Mrs E. B. Montgomery who typed the manuscript.

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Book review

Coronary Heart Disease: Clincal, Angiographic and Pathologic Profiles. By Z. Vlodaver, K. Amplatz, H. B. Burchell, J. E. Edwards, pp. xv+584, illust., 1976 (Springer-Verlag, New York, Heidelberg, Berlin), DM152.50/$62.50

This book is a timely contribution to medical literature, when coronary disease is claiming more and more clinical effort from clinicians and radiologists. The spectacular success of vein graft surgery has enormously broadened the scope of coronary arteriography, which now is by far the most commonly performed invasive investigation on the heart. As stated in the preface, the book presents a comprehensive picture of ischaemic heart disease to those who, either as practitioners or students, deal with the varied facets of this complex subject. It has meaning to the fields of clinical cardiology, radiology, thoracic surgery and pathology. The contents cover anatomy, technical aspects of arteriography, anatomical variations, pathology of obstructive disease with angiocardiographic-pathologic correlations, clinical correlations in angina and myocardial infarction and the results and complications of surgery.

The production is lavish, and in its 584 pages there are 1252 figures including 271 radiographs, the quality of which is excellent. Such a pity then that the authors should have rendered the text almost unreadable by the use of no less than 77 abbreviations for the commonly used words and phrases. Most of us know the meaning of ECG and LV, but how many would be familiar with FIP (fibrous intimal proliferation) and MuB (muscular branch), or know that C stands for catheter, Cl for clip, Oc for occlusion and St for stenosis. Despite this blemish on what is otherwise a superb book, it deserves to find its way on to the shelves of those working in this field, although the price will prove daunting for the individual.

S. REES.

1978, *British Journal of Radiology*, *51*, 24–28

Bone mineral measurement using an EMI scanner and standard methods: a comparative study

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ABSTRACT

The established techniques of scanning photon densitometry and radiographic microdensitometry for the analysis of bone mineral content are compared with results obtained using a modified EMI brain scanner. The EMI method shows significantly greater sensitivity to changes in bone density than either of the other two methods. This latter method also has the added advantage of being able to visualize and measure the density of trabecular bone, which is a very sensitive indicator of bone mineral changes.

Bone diseases such as osteoporosis result in an overall resorption of bone causing a reduction in bone tissue. This may be so severe that it presents as collapsed vertebrae or pathological fractures. Unfortunately, by the time these diseases become diagnostically apparent they are often very well established, even to the extent that there may be irreparable damage. Accurate methods of monitoring bone dynamics are therefore desirable. Conventional methods of bone mineral measurement include photon densitometry with γ rays pioneered by Cameron and Sorenson (1967) in the early sixties and more recently by West and Reed (1970), and also the more commonly used and older method of radiographic densitometry (Barnett and Nordin, 1961; Lachman and Whelan, 1936; Larsson, 1969). These well tried methods were compared under optimal conditions with a new method which utilizes a modified EMI brain scanner (Isherwood *et al.*, 1976).

MATERIALS AND METHODS

Young 1 kg ± 50 g female Dutch rabbits were used to establish an animal model in which osteoporosis was produced by means of the steroid cortisol.

Osteoporosis was induced in five rabbits by cortisol using a dose schedule of 2.5 mg/kg per day subcutaneously which according to Bartley (1968) and Blackwood (1969) would produce a loss of bone mass of between 40 and 60% after approximately 28 days. Five other rabbits were given an equal amount of cortisol vehicle and used as controls. All the rabbits were fed a normal diet, *i.e.* not calcium free. The effects of the cortisol administration were monitored by analysing the daily urinary calcium output of the rabbits. Twenty-four hour urine volumes were measured and samples taken to which 5 ml of dilute HCl was added to prevent calcium precipitation. Calcium concentrations were measured using an automatic absorption spectrometer.

After 28 days administration of cortisol, all the rabbits were sacrificed and their right hind limbs removed from the rest of the body. Fur, skin and some soft tissue were removed and the limbs were placed in cold storage so that autolytic changes would be minimal.

The bone mineral content of the right hind leg of each rabbit was measured by all three methods. In the isotope scanning and X-ray methods the legs were held in a Perspex water tank containing a rubber cuff (Fig. 1). The limbs were placed in the cuff and the tank filled with water.

Photon densitometric method

The radioactive source chosen was a point source of iodine 125 (27.5 keV). A collimated sodium iodide crystal and photomultiplier was used as detector. The collimators consisted of parallel holes in lead, 0.5 cm long and 1 mm diameter at the source and 2 cm long and 1 mm diameter at the detector. The basic design of the apparatus was that used by Cameron and Sorenson (1967). The limb was moved manually through the isotope beam on a specially

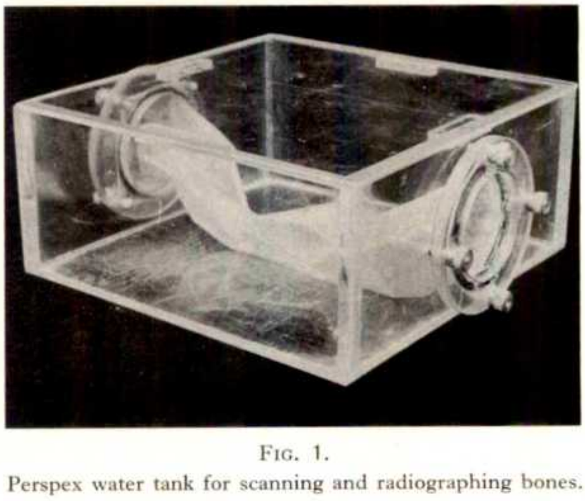

FIG. 1.

Perspex water tank for scanning and radiographing bones.

constructed table. The position of the scan on the leg was the same for each animal so that all the scans would be comparable, and counts were obtained at one millimeter intervals across the leg. The time for counting was such that approximately 10 000 pulses were registered for each interval. All scans were taken at a distance of 5 cm from the acetabulum and perpendicular to the long axis of the bone.

Radiographic microdensitometry method

Radiographs of limbs in the water-filled tank were taken at 40 kV and 160 mAs using Kodak KD547 film. A step wedge (Fig. 2), containing concentrated calcium chloride solution, was also placed in the tank adjacent to the limb for each exposure. Exposures were chosen so that the film densities over bone were within the linear range of the film as measured by the step wedge. The X-ray focus to film distance was 150 cm in each case and at this distance the calculated change in X-ray intensity across the film is less than 1%.

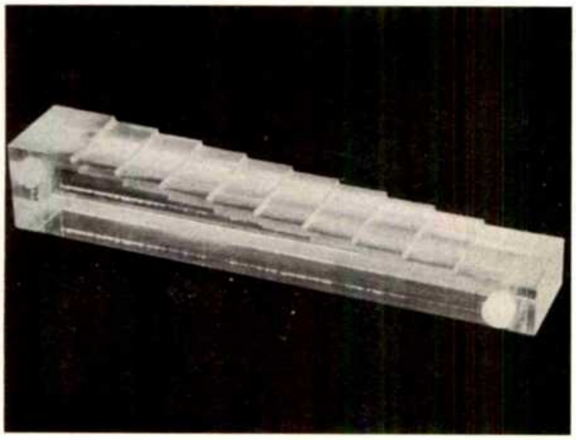

FIG. 2.

Calibration step wedge filled with calcium chloride solution.

All the X-ray films were developed in the same manner and on the same day. Density tracings were taken across the images of the bones with a Joyce-Loebl scanning microdensitometer at a distance of 5 cm from the acetabulum and perpendicular to the long axis of the bone. The step wedge was also scanned in each case.

EMI method

The scanner used was a prototype EMI brain scanner with additional apparatus to facilitate the scanning of the limbs (Isherwood *et al.*, 1976). Five rigid plastic tubes were cut to the same lengths and taped together. The limbs were placed in the tubes and the whole arrangement placed in a water-filled container which was positioned in the head bag of the EMI scanner. Each group was scanned in turn at a distance of 5 cm from the acetabulum. A visual record was obtained on Polaroid film together with a computer print-out of attenuation values.

RESULTS

One "normal" rabbit died and so results for only four normals are given.

Urinary calcium outputs

The mean urine calcium concentrations were calculated for each group. The mean for the control group was 3.2 mg/24 h with a standard deviation of 1.9 mg/24 h; the mean of the cortisol group was 32.5 mg/24 h with a standard deviation of 48.0 mg/24 h. Using a Student's T-test these are significantly different at the $P = 0.0015$ level.

Photon densitometry method

The average number of photons through the water alone (N_1) was calculated, for each scan, from five readings taken through the water alone. The minimum number of photons transmitted through the two

TABLE I

NORMAL AND CORTISOL TREATED BONE ATTENUATIONS USING THE PHOTON SCANNING TECHNIQUE

Normal controls			Cortisol treated		
Rabbit	Mean cortical ratio	Trabecular ratio	Rabbit	Mean cortical ratio	Trabecular ratio
1	0.749	0.515	1	0.645	0.451
2	0.669	0.489	2	0.563	0.383
3	0.742	0.562	3	0.627	0.301
4	0.769	0.477	4	0.656	0.450
			5	0.549	0.282
Mean	0.732	0.510	Mean	0.608	0.373
S.D.	0.044	0.038	S.D.	0.049	0.080

cortices and the maximum number through the mid-trabecular space (N_2) were determined and the ratios $ln\ (N_1/N_2)$ calculated for each animal of the two groups for both cortical and mid-trabecular positions. The results are given in Table I. Student's T-tests were performed to compare the normal and cortisol treated animals. The Student t value was 4.0 for cortical bone change and 3.4 for trabecular bone change, the corresponding P values being 0.025 and 0.01.

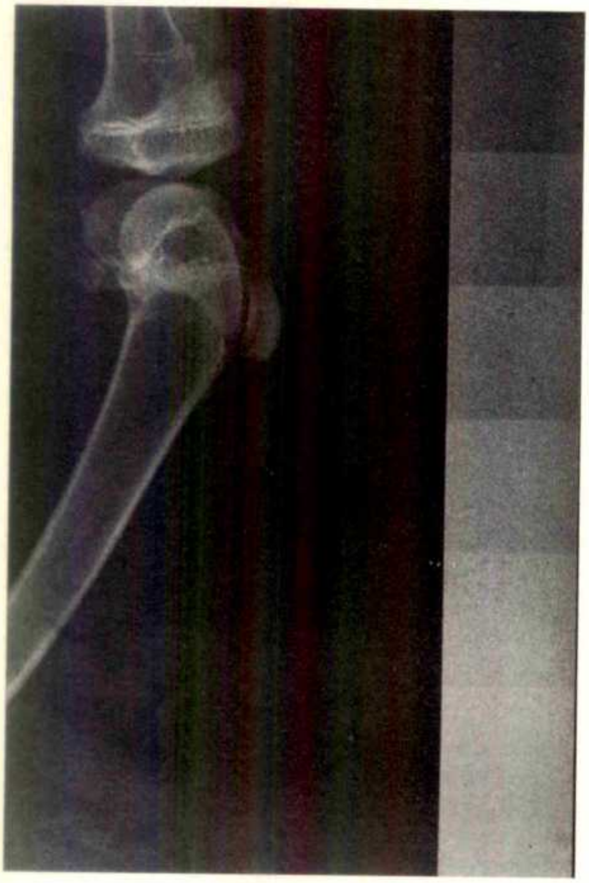

FIG. 3.

Radiographs of rabbit bone and calibration wedge.

Radiographic microdensitometry method

A typical radiograph is shown in Fig. 3. For each radiograph the transmission through the water tank T_1 was determined and also the maximum attenuated transmission through the two cortices and the minimum attenuated transmission through the mid-trabecular space T_2 were determined by measuring the optical density of the respective areas of film.

The ratios $ln\ (T_1/T_2)$ were again calculated and are shown in Table II. The Student t value was 4.1 for cortical bone change and 3.8 for trabecular bone change.

Although trabecular bone results are given for the above two methods it must be remembered that these values also contain a contribution from the overlying cortical bone.

EMI method

An EMI scan is shown in Fig. 4. The bone positions on the corresponding computer print-outs were identified and rectangles constructed around any numbers greater than 40 at each bone position on the scan. The definitive bone edge cannot be ascribed to a single threshold attenuation coefficient because of the effect of the adjacent soft tissue. Consequently a set of threshold values are used above which the values of attenuation coefficient are known to correspond to bone. If the sum of all the attenuation values above these thresholds in the region of the bone is taken and a linear extrapolation carried out, the extrapolated sum of the attenuation values at zero threshold can be determined. This extrapolated value can then be used as a measure of

TABLE II

NORMAL AND CORTISOL TREATED BONE ATTENUATIONS USING THE RADIOGRAPHIC TECHNIQUE

Normal controls			Cortisol treated		
Rabbit	Mean cortical ratio	Trabecular ratio	Rabbit	Mean cortical ratio	Trabecular ratio
1	0.808	0.427	1	0.581	0.262
2	0.950	0.558	2	0.558	0.205
3	0.666	0.348	3	0.588	0.308
4	0.965	0.596	4	0.540	0.217
			5	0.485	0.264
Mean	0.847	0.482	Mean	0.550	0.251
S.D.	0.140	0.115	S.D.	0.041	0.041

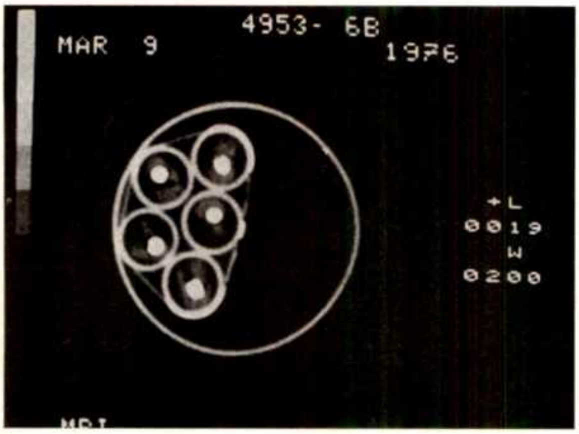

FIG. 4.
EMI scan of rabbit limbs.

TABLE III
NORMAL AND CORTISOL TREATED BONE ATTENUATION VALUES USING THE EMI SCANNING TECHNIQUES

Normal controls		Cortisol treated	
Rabbit	Extrapolated totals	Rabbit	Extrapolated totals
1	8280	1	6130
2	7760	2	5150
3	7560	3	6250
4	8440	4	5406
		5	6130
Mean	8010	Mean	5813
S.D.	417	S.D.	500

bone mineral content. Thus all the numbers contained within the rectangles were fed into a computer which was programmed to produce sums of numbers which were > 40, > 60, > 80, > 100 and > 120.

These totals were then plotted against thresholds of 40, 60, 80, 100 and 120 for each animal and the graphs extrapolated to find the total EMI number above zero (Isherwood *et al.*, 1976). The extrapolated totals are given in Table III. Student's T-tests were performed on the extrapolated totals and the *t* value for bone change was 7.2.

DISCUSSION

Student's T-tests were performed on all the results. The *t* value represents the difference in the mean values divided by the standard error of the difference. The error of the difference in experimentation arise from two sources: (1) the spread of values due to variations within a population, and (2) measurement errors.

As the same population was utilized in each method of bone mineral determination, the error produced by this variation is a common factor. The differences in the *t* values therefore reflect errors in the method of measurement. The greater the *t* value the more sensitive is the method in detecting slight alterations in mineralization. From consideration of the *t* values it can easily be seen that by far the most sensitive method for detecting changes in bone mineralization is that of EMI scanning for which the *t* value is more than double that for the other methods. The isotopic and radiographic methods are roughly comparable in sensitivity; this contrasts with the findings of Colbert *et al.* (1970). The radiographs in this experiment were, however, developed on the same day and so daily variations in development (Vose, 1965) were not experienced.

At the same time a study involving the same animals and methods but with the additional use of the calcium chloride solution calibrator was undertaken. The results obtained from this study were not significantly different from those of the original study without a calibrator. This does not mean, however, that the use of a calibrator should be abandoned as in a longitudinal study it may prove more useful.

The EMI method is the only procedure by which trabecular bone is visible as an entirely separate entity, as in both the other methods it is seen only in combination with the surrounding cortical bone. If the lowest and highest EMI numbers from the print-out are analysed and taken to represent the trabecular and cortical bone respectively, the relative change in mineralization between the two groups was 59% in the trabecular space but in the cortical region only 32%. This result would appear to reinforce the idea that trabecular bone, as a consequence of its vascularity, is affected by bone demineralizing disease more than cortical bone and therefore is a more sensitive indicator of bone dynamics than cortical bone.

The similarity of *t* values between the photon beam scanning and radiographic methods shows that the usefulness of the radiographic method, devalued in recent years, should be re-examined, as this method has the advantage of simplicity and speed and is much easier to perform clinically. In addition it is possible to obtain a higher degree of positional accuracy in the radiographic method than with either of the other two methods because the measurements can be accurately related to bone markers on the radiograph.

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Book review

Recent Results in Cancer Research Vol. 55 Cancer Active Immunotherapy, Immunoprophylaxis and Immunorestoration. By G. Mathé, pp. 405, 1976 (Springer-Verlag, Berlin-Heidelberg, New York), $29.60.

Few oncologists have sought to exploit immunotherapy as an adjunct to other forms of cancer treatment with quite the same degree of assiduity as Professor Georges Mathé. During the past 15 years his efforts, particularly in the therapy of leukaemia, both clinical and experimental, have been largely unrivalled. Such credentials might lead one to anticipate a uniquely authoritative account of the subject but in some respects the present volume leaves those expectations unfulfilled.

The unusual style of presentation takes the form of a sequence of short paragraphs and the text reads as an amalgamation of frequently unrelated and sometimes erroneously interpreted citations from a vast literature, with little effective synthesis or literary merit—a particularly disappointing feature for one whose command of the English language is proverbial. There is uncritical use of certain technical terms (the prefix "immuno-", for example, turns up with alarming ubiquity) and numerous type-setting errors disclose hasty preparation. Despite these limitations, however, the basic flaw is a conceptual one. Notwithstanding the many animal models (not necessarily confined to tumours of "spontaneous" origin) where lack of neoantigenicity militates against any prospect of immunological control *in vivo*, the tumour specific antigenicity of human neoplasms appears to be taken for granted, providing the rationale that immune responses thereto can be harnessed in favour of the host. Unfortunately, hard evidence for the former assumption, despite heroic efforts by many laboratories, still remains elusive; and it is not surprising that immunotherapy protocols based on the putative existence of such antigens have failed to yield decisive results. Clinicians with an interest in malignant melanoma will thus find little justification for Mathé's claim that the clinical efficacy of immunotherapy as an adjunct to surgery in this disease is already established.

In much of the text dealing with human malignancy, Mathé appears to be unmoved by the marked changes which have occurred in the climate of tumour immunology during the past few years, wherein the optimism of the 1960s has been replaced by a more healthy realism, and the notions which inspired well-intentioned but misguided forays into immunotherapy replaced by a more pragmatic approach to the problem. Indeed there is much to commend the view that precise characterization of human tumour-related antigens and the immune response to them is a necessary requirement before questions of clinical significance and therapeutic application can be profitably addressed.

In other respects the scope of the book is considerable. There are useful, if somewhat cursory, chapters on tumour associated antigens in defined experimental systems and on fundamental aspects of the immune response. The (unconvincing) results of systemic active immunotherapy (the author's *tour de force*) are itemized for the multiplicity of human neoplasms and local active "immunotherapy" is, appropriately, given separate treatment. A chapter on "developmental pharmacology" attempts to deal with the plethora of approaches to the immunotherapy of cancer and others with adverse effects arising therefrom, putative mechanisms of failure (?) and immunorestoration. In all, a comprehensive treatise but lacking the critical sense of balance which is mandatory in this controversial field.

M. Moore.

1978, *British Journal of Radiology*, *51*, 29–34

JANUARY 1978

Penetrameter cassette calibration to 400 kV and effects of extra-focal radiation when measuring tube filtration

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ABSTRACT

The penetrameter cassette, when used with suitable filters and calibrated against the same average wave form, can detect changes of less than 1 kV in the range 20–50 kV, 1 kV from 50–100 and from 1–4 kV from 100–400 kV. Problems of calibration are discussed together with the necessity to use a suitable shutter with equipment which has a significant build-up and decay time during which the radiation quality may be varying. Extra-focal radiation does not normally present a significant problem in the measurement of kV, but when the penetrameter is used to measure inherent or total filtration extra-focal radiation can be a problem and may be similar in degree to the effects of varying target angles.

When used to determine filtration, the generator used for calibration of the penetrameter and the one being measured should be adjusted to have the same target angle and similar degrees of extra-focal radiation by altering the size of the tube aperture as close to the focal spot as practicable. The results presented confirm the accuracy and convenience of the penetrameter for the measurement of kV and filtration over the extended range of energies.

The question is often asked as to whether the penetrameter cassette (Ardran and Crooks, 1967, 1968) can be used and is accurate above 100 kV: it had originally been checked that the cassette could be used with isotopes such as thulium 170 or cobalt 60 and therefore responded to radiation in the high energy range.

Provided the penetrameter is used with suitable filters and is calibrated against the same voltage wave-form as that being estimated, the penetrameter can detect changes of less than 1 kV in the range 20 to 50 kV, 1 kV from 50 to 100 kV and from 1 to 4 kV from 100 to 400 kV. Different "constant potential" generators may have different voltage wave-forms, different X-ray tubes will have different characteristics and calibration methods will also have their limits of accuracy. Problems may also arise when the method employed for calibration prevents simultaneous checking against the penetrameter. Setting up the equipment with the appropriate factors on another occasion may not result in an identical quality of radiation. Other workers using the penetrameter cassette have amply confirmed our original claims as to its value and accuracy up to 100 kV (Hospital Physicists Association, 1975). It can be used with molybdenum target tubes using calibration curves for tungsten targets (Ardran and Crooks, 1973).

We have found that provided the radiation source can be set up on different occasions to give the identical quality of radiation (*e.g.* an americium 241 source) the penetrameter consistently gives identical CRN values. Potential dividers, spark gaps and spectrometry do not necessarily indicate similar values of kVp in apparently identical situations. These discrepancies are at present under investigation, but in view of the fact that it may take a considerable time to understand them fully we considered it useful to indicate that the penetrameter will give consistent and accurate results for equipment with truly identical characteristics. We would point out that when the penetrameter indicates that two sets of equipment have the same effective kV they will give the same radiographic results for all practical purposes.

RESULTS OF CALIBRATIONS

Figure 1 shows typical calibration curves for our penetrameter. In the energy range 20 to 50 kV the initial filtration close to the tube was 0.25 mm Cu additional to the inherent. From 40 to 300 kV the initial filtration was 1.5 mm Cu and from 100 to 400 kV the initial filtration was 4 mm Cu. The graphs have been plotted on double log paper in order to limit the size for the purpose of publication. They are not intended for use by others who will require their own curves: in practice we use graphs plotted on linear scales of adequate dimensions for accuracy. The standard cassette now uses copper reference numbers up to 196 thousandths of an inch (5.0 mm) Cu; to extend the range to about 400 kV an additional strip of copper 40 thousandths of an inch (1 mm) thick is laid over the step wedge and thus 196 becomes 236.

In the 20 to 50 kV range the results were obtained from a Siemens beryllium window Dermopan generator and also the Harwell E.12 generator (inherent filtration 0.1 mm Al). In the range 50 to 100 kV the Siemens Gigantos generator (inherent filtration 0.62 mm Al equivalent) and the Harwell E.12 generator were used. The E.12 and Gigantos generators had been checked spectrometrically (Marshall *et al.*, 1975). In the range 80 to 250 kV the results were

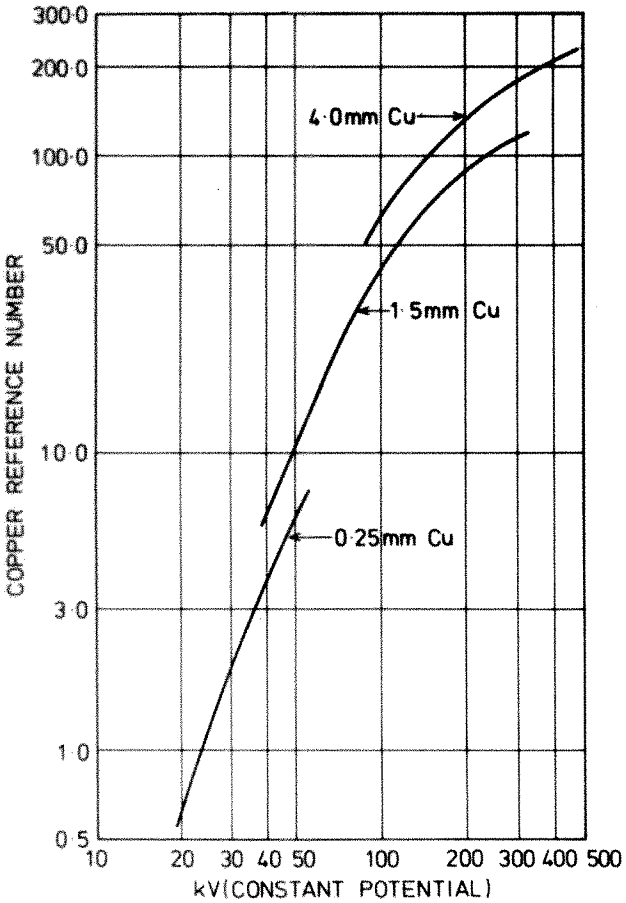

Fig. 1.

Graphs plotting copper reference number (thousandths of an inch or 0.0254 mm of Cu) against kV (constant potential). See text for details.

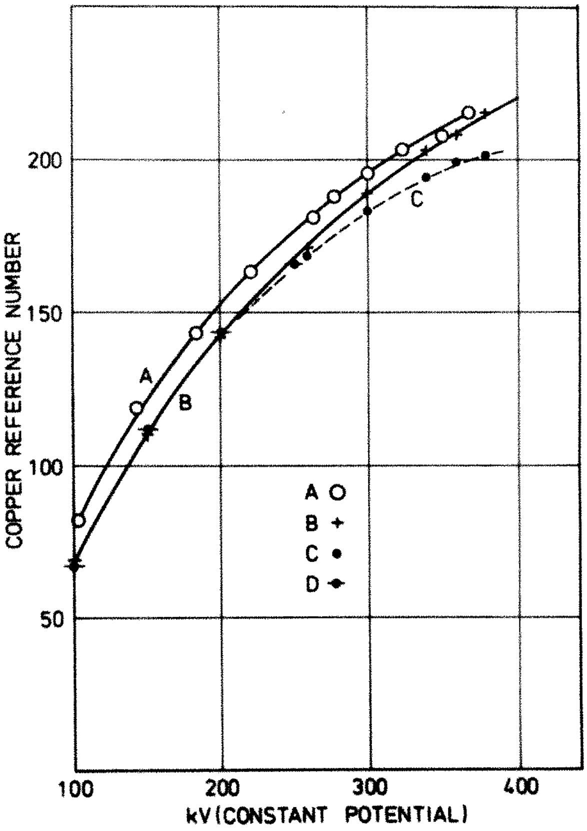

Fig. 2.

Curve A (○) is the plot of CRN against kV for a Pantak nominally constant potential generator which had been spectrometrically calibrated; the shutter described in the text was used for the CRN measurements. The curve below the above shows the experimental points for another new Pantak generator recently calibrated by spark gap, (B, +) showing agreement with the results obtained from the Marconi C.E.G.B. spectrometrically calibrated generator (D, -●-). The CRN measurements with this apparatus were obtained using a very simple in and out shutter. The dotted curve C (●) gives the experimental points with the Pantak spark gap calibrated generator (B) when no shutter was used to terminate the exposure.

obtained from a Marconi constant potential generator at the Berkeley dose calibration facility of the C.E.G.B. which had been spectrometrically calibrated. The 100 to 400 kV calibration was obtained from two Pantak 400 kV constant potential generators: one of these was at Harwell and was spectrometrically calibrated while the other was a new generator at Messrs. Pantak which was calibrated using a spark gap.

Unless a suitable lead shutter is used with generators such as the Pantak (which were not designed for short exposure work) calibrations at the higher kilovoltages are unsatisfactory due to the time taken for the X-ray output to build-up and decay.

A lead shutter has been made to ensure that short exposures can be given to the penetrameter with a uniform field. The X-ray beam was restricted with a lead diaphragm so as just to cover the penetrameter at the distance used. The aperture was closed by a 1×5×5 cm lead shield. The generator was switched on and time allowed for the radiation beam to stabilize. To initiate the exposure the aperture was uncovered by pulling the lead shield across it by a solenoid. To terminate the exposure after a suitable interval, another similar lead block was pulled by another solenoid across the aperture (to close it) in the same direction and speed so that each portion of the penetrameter received the same exposure. Thus the shutter is used to eliminate the build-up and decay time with this type of generator. When fluoroscopy circuits of other generators are being calibrated a shutter may also be necessary if the build-up and decay time are a significant part of the exposure required. Fluoroscopy circuits may be necessary for spectrometry or other methods of calibration when low outputs are required. When comparing these calibrations with those obtained by the penetrameter, a shutter may be required so that only stable conditions are recorded.

In diagnostic equipment very short exposures can alter the apparent measured kV because of the irregular build-up period (Ardran and Crooks, 1973). This situation does not of course apply during

TABLE I

APPARENT VARIATION OF TUBE FILTRATION DUE TO THE INFLUENCE OF EXTRA-FOCAL RADIATION

Area of anode from which focal and extra focal radiation is received (Fig. 3) cm	kV	mA	Exposure time (sec)	Distance (cm)	Exposure mR	CRN	Effective filtration mm Al equiv.
0 0.5 × 0.5	80	12	0.01	350	1.1	5.9	1.7
A 1.0 × 0.5	80	12	0.01	350	1.21	5.68	1.65
B 2.0 × 0.5	80	12	0.01	350	1.288	5.57	1.5
C 4.8 × 0.5	80	12	0.01	350	1.42	5.3	1.3

Measurements made with the tube port restricted as in Figs. 3A, B and C and also 0 with the beam restricted further. Manufacturer's nominal inherent filtration 1.0 mm Al equivalent when tube was new: present age 15 years: 50,000 exposures.

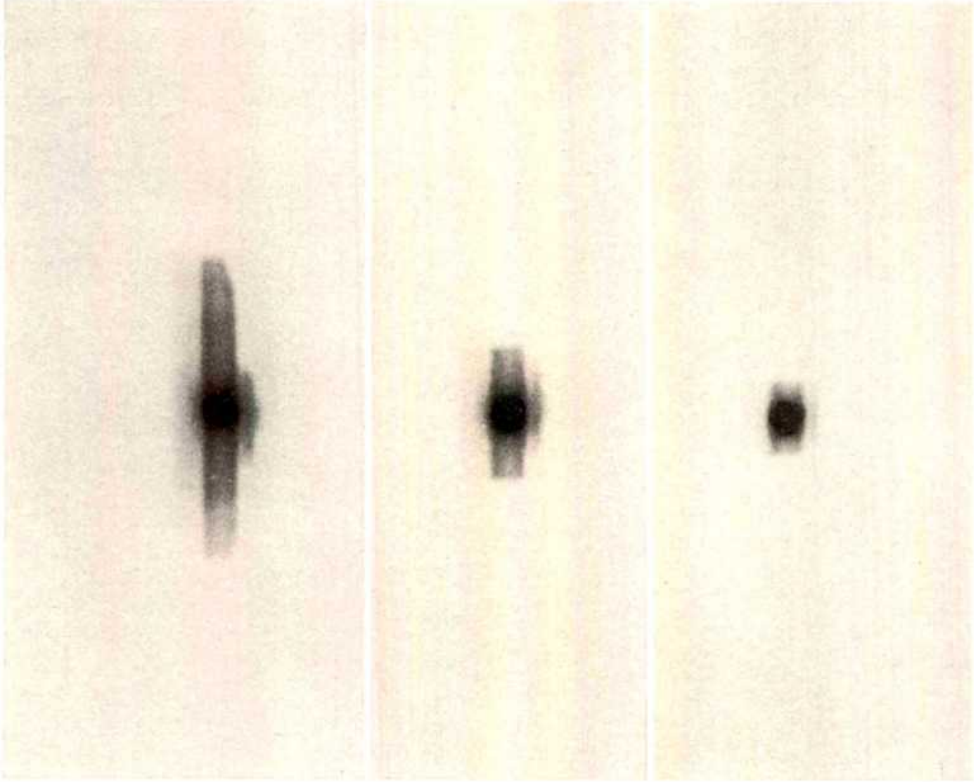

FIG. 3.

"Pinhole" (1.0 mm hole) radiographs of source of X-ray emission through tube port made on non-screen film. (A) With the beam restricted at the tube port to allow rays from an area of the anode 1 × 0.5 cm to reach the film. (B) Beam restricted at the tube port to an effective area of 2 × 0.5 cm. (C) Beam restricted at the tube port to 4.8 × 0.5 cm. We have ignored extra focal radiation from sources other than the anode, since the proportions are very small.

normal calibration by the manufacturers for which stabilized conditions are used.

The experimental points obtained with the three generators used in the highest energy range are given in Fig. 2. It will be seen that the penetrameter records small changes in kV but different curves are obtained with different generators and methods of calibration. An example of the discrepancies obtained when a suitable shutter is not used is also illustrated.

Extra-focal radiation does not usually present a great problem in kV calibration or measurement because of the heavy initial filtration, and errors of more than 1 kV are unlikely at 100 kV. When the beam has been restricted at the tube port as close to the target as possible (Ardran, 1957; Ardran *et al.*, 1964) the residual off-focus radiation present in the beam is a few per cent of the total beam. When there is no restriction of the beam at the tube port the off-focus content of the useful beam may be 20% or more.

Measurement of Tube Filtration

If the penetrameter is used to measure total or inherent filtration, extra-focal or off-focus radiation must be similar in calibrated and tested X-ray tubes or significant errors will occur.

We have previously described (Ardran and Crooks, 1972) how, when using inferential methods to measure inherent filtration, the values are affected by target angle, the effects of target filtration being added to those of inherent filtration. The effects of different amounts of extra-focal radiation are also of importance (Gibson *et al.*, 1975). The spectrum and intensity of extra-focal radiation has recently been investigated by Birch (1976). Since the amount of extra-focal radiation will alter the first half-value layer, it will obviously affect the results of any inferential method of measuring filtration unless the amounts are the same in the calibrated tube and in the tube being measured.

Table I gives some measurements of the inherent filtration of a tube with varying degrees of restriction of the tube port. The larger the aperture the more extra-focal radiation from the anode is contained in the beam. This lowers the h.v.l. and gives rise to apparently reduced inherent filtration. The values given were obtained using the penetrameter as described for this purpose (Ardran and Crooks, 1972). The values obtained from our calibration

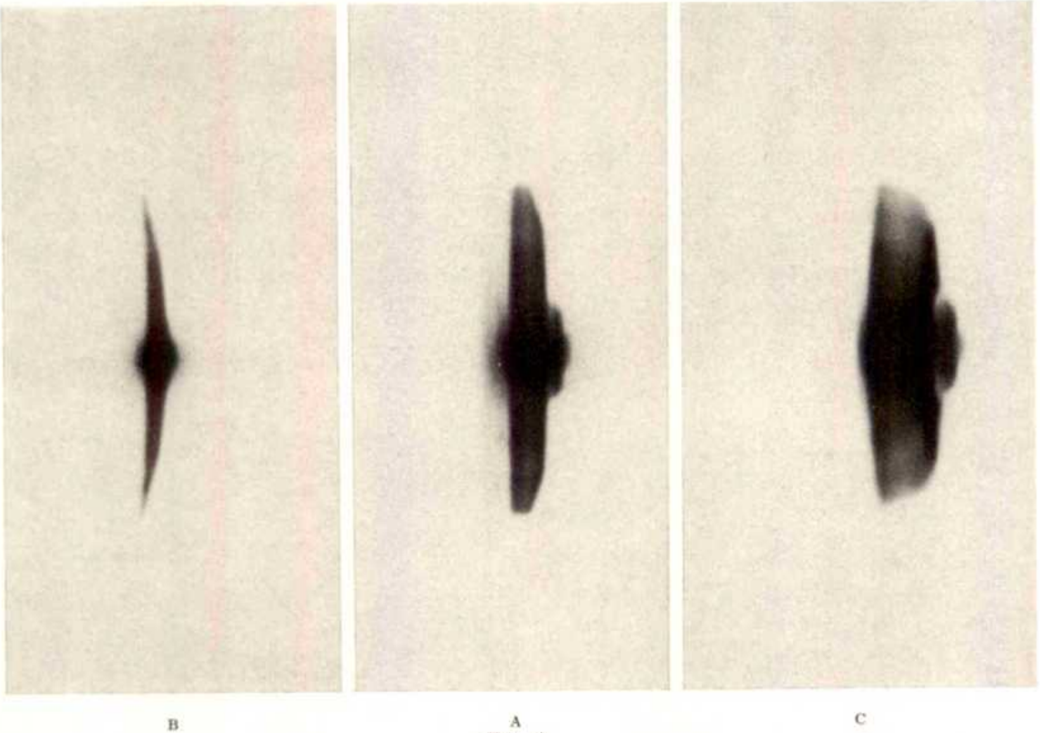

Fig. 4.

"Pinhole" radiographs as in Fig. 3 to cover the whole diameter of the anode (A) simultaneously using two further "pinholes" (B and C) on either side of the central pinhole to show the anode extra-focal radiation at different angles. The pinhole B is to the anode side of the central pinhole A and C is to the cathode side.

curves have been checked by adding the appropriate amounts of aluminium to the beams from the wider apertures when the beam quality, as determined by the CRN method, becomes the same as with the smallest aperture. Neglect of ensuring similar quantities of extra-focal radiation may lead to errors of up to 0.5 mm Al equivalent when estimating tube filtration. Unpublished observations have indicated that when the tube is tilted so that the effective target angle is changed, the percentage of off-focus radiation is the same. The effects of hardening of the beam by altering the tube angle can be distinguished from the effects of off-focus radiation by carrying out experiments with the tube tilted at different angles, with very small and with larger apertures.

We have previously shown (Ardran and Crooks, 1972) that changing the effective target angle from 17 deg to 10 deg by tilting the tube hardened the beam at 80 kV by at least 0.25 mm Al equivalent; this value may be increased with old, roughened or pitted targets. Table I shows that reducing off-focus radiation by changing the tube aperture from the conditions in (B) to (A) hardened the beam by 0.15 mm Al; thus for these conditions the effects of target angle in hardening the beam are greater than the off-focus effects. Different hardening values will be obtained with other changes in target angle or with different amounts of off-focus reduction. The examples given above are commonly found in practice.

Figures 3 to 5 are large pinhole radiographs illustrating the degrees of beam restriction used in Table I. In the tubes examined the main extra-focal contribution is from the anode disc and nut and extra-focal radiation from other sources within the tube is relatively insignificant.

CONCLUSIONS

We consider that the penetrameter cassette is accurate for practical purposes and can be used with X rays from 20 to at least 400 kV. We consider it to be accurate and convenient for the measurement of inherent or total filtration provided accurate calibration curves are prepared and the problems connected with target angle and extra-focal radiation are dealt with.

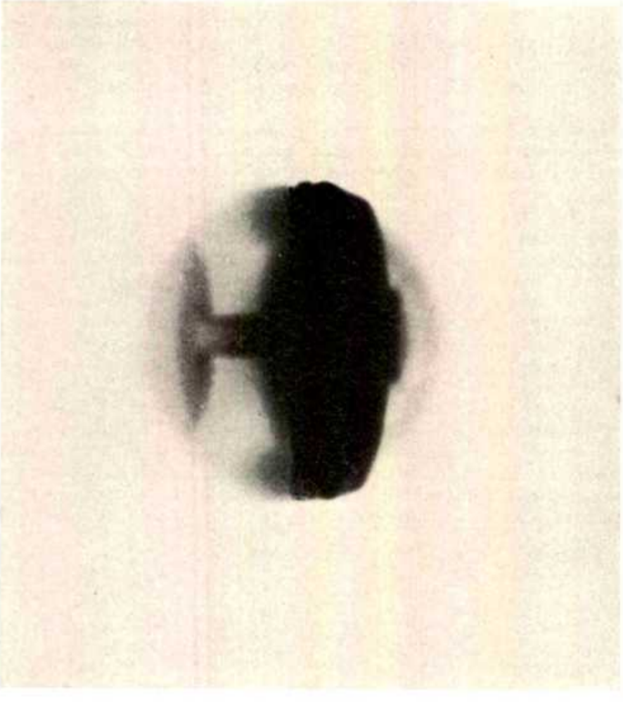

FIG. 5.

"Pinhole" radiograph exposed with a film-screen combination giving greater sensitivity to show the anode spindle. It is estimated that the extra-focal radiation from sources other than the anode disc and bolt are relatively insignificant in most tubes.

ACKNOWLEDGMENTS

We are grateful to Messrs. Gibson, Peaple and Marshall for spectrometric calibration of one of the Pantak 400 kV generators and to Drs. B. M. Wheatley and I. Thompson of the Berkeley Laboratories of C.E.G.B. for allowing us to use their Marconi calibrated generator. Our thanks are also due to Messrs. Pantak for facilities to calibrate our cassette to 400 kV using a new generator recently calibrated by spark gap.

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Book review

Structural Shielding Design and Evaluation for Medical Use of X rays and Gamma rays of Energies up to 10 MeV. NCRP Report No. 49, pp. 126, 1976 (National Council on Radiation Protection and Measurements, Washington, USA), $3.50.

This report is essentially a revised version of the earlier report number 34 (1970) which it supersedes. Its title is an explicit statement of its contents which are divided into eight chapters and five appendices.

After an introductory chapter which "sets the scene" by specifying the objectives of the detailed, factual information provided by the report, the second chapter presents the general principles concerning the purposes and requirements of protective barriers. The third chapter lists the properties of the various forms of the more commonly used barrier materials: lead, concrete, glass and liquids. The fourth chapter gives details of specific aspects of barrier construction such as, for example, joints, corners, door edges and surroundings, baffled openings, entry mazes and observation windows. The chapter is extremely well illustrated by relevant and clear diagrams.

The next three chapters provide specific details relevant to installations used for diagnostic, external beam therapy and brachytherapy purposes. The final chapter specifies the need for a radiation protection survey. It points out the actions to be taken before, during and after the construction and gives brief information about the measurements to be performed. The chapter concludes with a clear statement of the required contents of the radiation protection survey report.

As is so often the case with this kind of publication, the appendices, which comprise more than 70% of the total text, provide a large quantity of essential, specific details. Appendix A lists the definitions of the special terms used in the report and its appendices. Appendix B is a 14-page description of the methods and assumptions used in the calculation of both primary and secondary barriers in practical circumstances. Of particular value are appendices C and D which provide, respectively, 29 tables of data and 17 graphs. The graphs are of the percentage transmission by the various barrier materials of the wide range of photon energies covered by the report. These are presented in semi-logarithmic form. Although the scale used is rather small, the graphs are perfectly easy to read. Nevertheless, they are also available separately on a larger scale. This is clearly advantageous and a practice to be commended.

The report concludes with a single-page chapter which lists the architectural and equipment information to be supplied to the qualified expert for use in shielding design, and finally an excellent index.

There is no doubt that, like its predecessor report 34, the present report will be of immense value to and should be in the possession of all who are concerned with the design and testing of radiological installations. At $3.50 U.S. per copy it is one of today's bargains.

J. B. MASSEY.

1978, *British Journal of Radiology*, *51*, 35–40 JANUARY 1978

Clinical radionuclide perfusion lymphangiography

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ABSTRACT

In an initial pilot study technetium-99m-labelled human serum albumin was perfused directly into bipedal lymphatic cannulae prior to a standard lymphangiogram, in order to assess rapidly normal and abnormal lymph flow patterns in the lower extremity, pelvic and para-aortic lymph chains.

A continuing study of these patients has lent further support to the hypothesis that the radionuclide perfusion study, when negative, may prove more accurate in some patients than the standard lymphangiogram in predicting the clinical course and/or the results of histopathological lymph node examination. The radionuclide technique also seems to meet, in this preliminary evaluation, the requirements for a pre-lymphangiogram screening study, particularly for use in high-risk patients.

Experimental and initial clinical results with a new radionuclide imaging technique to complement the standard Ethiodol lymphangiogram were first reported two years ago (Steckel *et al.*, 1975). Results for thirteen experimental subjects and twenty-one patients who were subjected both to radionuclide perfusion lymphangiograms and standard Ethiodol lymphangiograms were reported. The rapid radionuclide perfusion technique, which is performed by means of direct cannulation of pedal lymphatic vessels (see below), should be distinguished from other, more commonly used radionuclide lymphographic methods which employ interstitial injections of a labelled colloid (Fairbanks, 1972; Gates *et al.*, 1972; Herting *et al.*, 1970; Kazem *et al.*, 1968; Perlman, 1970; Sage *et al.*, 1960; Winkel *et al.*, 1965). Pathological proof was available in the twenty-one patients initially reported, and it was concluded that the radionuclide perfusion lymphangiogram might be an effective screening study for determining if a standard (Ethiodol) lymphangiogram were necessary, particularly in high-risk patients (Steckel *et al.*, 1975). The radionuclide perfusion study correctly identified as "positive" all patients who subsequently had positive histological evidence of tumour in pelvic or retroperitoneal lymph nodes. In addition, the radionuclide study correctly identified as "positive" two patients with histological proof of lymph node involvement who had falsely negative Ethiodol lymphangiograms. Nevertheless, two patients in this series with a negative standard lymphangiogram and a negative pathological examination were incorrectly identified as "positive" by the radionuclide study. Despite these two "false-positive" cases, the radionuclide perfusion technique seemed in this initial series to fulfil the requirements for a relatively innocuous "screening study" to be used prior to a standard (Ethiodol) lymphangiogram. Whereas the standard Ethiodol lymphangiogram continued, as expected, to provide more detailed morphological information about alterations in lymph node and vascular architecture, the radionuclide technique seemed to emphasize abnormalities in lymph flow in the lower extremities, the pelvis and the retroperitoneum. In view of this, another possiblity was that the two examinations might ultimately complement each other by providing additional information for tumour diagnosis and staging. It is possible that small and otherwise undetectable tumour burdens located strategically in the paths of normal lymph flow might lead to early alterations in the flow patterns which would be detectable by the pefusion technique.

Additional follow-up data are now available from the 41 patients in our initial pilot series, and these data are the subject of the present report. Twenty-four patients have pathological proof of pelvic or retroperitoneal lymph node involvement (or non-involvement) by tumour, and an additional ten cases have been followed clinically (without histological examination) for more than 18 months after their radionuclide perfusion lymphangiogram and Ethiodol lymphangiogram. In the latter ten cases, the subsequent clinical courses can now be correlated with findings on the preceding lymphangiographic studies.

MATERIALS AND METHODS

A total of 41 patients have been examined in this preliminary series with a radionuclide perfusion lymphangiogram, followed directly by a standard Ethiodol study. The same bipedal lymphatic cannulae which were introduced in standard fashion under local anesthesia were used for both studies. Details of procedure have been described earlier (Steckel *et al.*, 1975), and only a brief summary is presented here.

Lymphatic cannulae were introduced in the dorsa of both feet under local anesthesia, as with an ordinary lymphangiogram study. The patient was then positioned supine over a gamma camera,* and 4 ml of $^{99}Tc^{m}$-labelled human serum albumin (containing approximately 2 mCi labelled HSA) was perfused simultaneously at a rate of 0.2 ml per minute into each lymphatic cannula. Prior to perfusion, protein-unbound pertechnetate was removed by filtration through an anion exchange resin. During each lymphatic perfusion, the rapid ascent of technetium-labelled albumin was followed (by direct viewing on an oscilloscope screen and by serial Polaroid photographs) up the lymphatic chains of both legs and thighs, through the pelvic and peri-aortic chains, and finally into the thoracic duct (Fig. 1A). Criteria for interpreting the radionuclide perfusion study have been described earlier (Steckel *et al.*, 1975), but the primary abnormality observed is obstruction to flow with delay in filling of normal lymphatic pathways, sometimes accompanied by lymph node enlargement (Fig. 1B). The time normally required for ascent of the perfused radionuclide through the pelvic and peri-aortic lymphatics to the level of the cisterna chyli is in the range 30 to 60 minutes for normal studies. Although several patients experienced minor discomfort, described as "tightness" in the calves and thighs during the first few minutes of perfusion, no untoward reactions were observed in any of the 41 patients studied. Following completion of each radionuclide perfusion and imaging of the pelvic and peri-aortic lymphatics (and often the thoracic duct as well), the patient was moved on a stretcher to the lymphangiogram radiographic room with the lymphatic cannulae still in place, and a standard Ethiodol lymphangiogram was performed using the same cannulae.

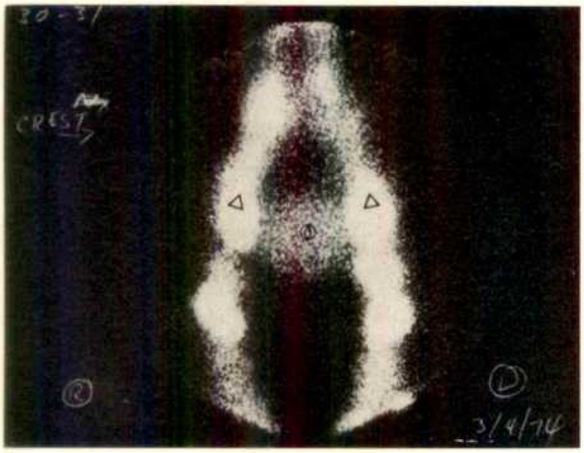

Fig. 1A.

Illustrative normal radionuclide perfusion lymphangiogram in a young woman (C.G., in Table I) with adenocarcinoma of vagina (mother of patient had received DES during gestation). Note radionuclide concentrations in normal femoral, iliac (△) and aortic bifurcation lymphatic vessels and nodes bilaterally. Some free pertechnetate has also been excreted into the bladder (mid-line ◎).

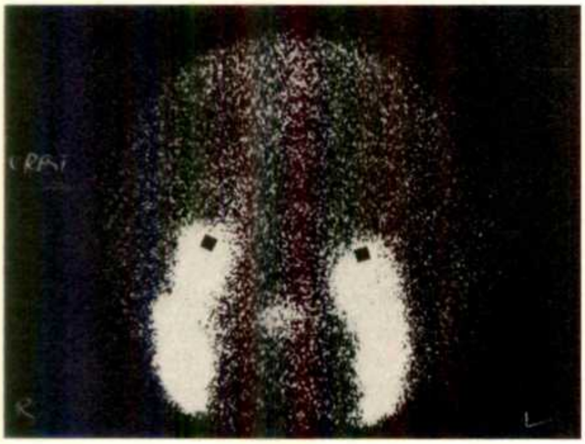

Fig. 1B.

Illustrative abnormal radionuclide perfusion lymphangiogram (R.B., in Table I), showing bilateral obstructions (■) to proximal lymph flow at the level of external iliac nodes. The standard Ethiodol lymphangiogram, as well as subsequent autopsy examination, revealed massive, bilateral pelvic lymph node replacement by Hodgkin's tumour.

Results

Of the 41 patients studied, 24 now have histological confirmation of tumour involvement (or non-involvement) of the pelvic and peri-aortic lymph nodes. These patients have been divided into two subgroups for further analysis:

Subgroup (1)—In 17 of these 24 patients, the radionuclide perfusion examination, the standard Ethiodol lymphangiogram, and the subsequent histological lymph node examination were all in agreement (Table I).

Subgroup (2)—In seven of these 24 histologically proven patients, one of the three listed studies was in disagreement with the other two (Table II).

In an additional ten patients, histological examination of the lymph nodes has not been performed. These patients have been followed clinically for a period of 18 months or more, and the results of their radionuclide perfusion study and standard Ethiodol lymphangiogram can now be correlated with their subsequent clinical course. These ten clinically-followed patients are divided in turn into two subgroups:

Subgroup (3)—In five of the ten patients the radionuclide perfusion study and the standard Ethiodol lymphangiogram were in agreement with

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*Picker Dynacamera IIb.

TABLE I

PATHOLOGICALLY-PROVED CASES, IN WHICH THE RADIONUCLIDE STUDY, THE STANDARD ETHIODOL LYMPHANGIOGRAM, AND THE LYMPH NODE HISTOLOGY WERE ALL IN AGREEMENT

Patient	Final diagnosis	Result of radionuclide study	Result of Ethiodol lymphangiogram	Result of histological lymph node examination
K.M.	Ca Cervix	Negative	Negative	Negative
M.T	Ca Cervix	Negative	Negative	Negative
E.H	Ca Cervix	Positive	Positive	Positive
M.B.	Hodgkin's	Negative	Negative	Negative
C.C.	Ca Cervix	Negative	Negative	Negative
A.H.	Hodgkin's	Positive	Positive	Positive
H.M.	N-H L*	Positive	Positive	Positive
G. Car	Hodgkin's	Positive	Positive	Positive
C.K.-T.	Ca Colon	Positive	Positive	Positive
T.S.	Ca Cervix	Negative	Negative	Negative
M.S.	Ca Cervix	Negative	Negative	Negative
V.S.	Ca Ovary	Negative	Negative	Negative
R.B.	Hodgkin's	Positive	Positive	Positive
L.S.	Ca Cervix	Negative	Negative	Negative
G. Cas	N-H L*	Positive	Positive	Positive
I.B.	Ca Urethra	Negative	Negative	Negative
G.G.	Ca Vagina	Negative	Negative	Negative

*Non-Hodgkin's lymphoma

TABLE II

PATHOLOGICALLY-PROVED CASES IN WHICH ONE STUDY WAS IN DISAGREEMENT WITH THE OTHER TWO STUDIES

Patient	Final diagnosis	Result of radionuclide study	Result of Ethiodol lymphangiogram	Result of histological lymph node examination
B.L.	N-H L*	Positive	Negative	Positive
M.B.	Ca Cervix	Positive	Negative	Positive
D.M.	Ca Vulva	Positive	Negative	Positive
A.M.	Ca Cervix	Negative	Positive	Negative
M.P.	Ca Cervix	Negative	Positive	Negative
B.W.	Adeno Ca (? Ovary)†	Positive	Negative	Negative
R.F.	"FUO"	Positive	Negative	Negative

*Non-Hodgkin's lymphoma
†Studies were done after good local response of tumour to pelvic irradiation.

TABLE III

CLINICALLY-FOLLOWED CASES*, IN WHICH THE RADIONUCLIDE STUDY AND THE STANDARD ETHIODOL LYMPHANGIOGRAM WERE BOTH IN AGREEMENT

Patient	Final diagnosis	Result of radionuclide study	Result of Ethiodol lymphangiogram	Clinical follow-up (length of follow-up period)
A.H.	Hodgkin's	Negative	Negative	N.E.D.‡(3 years)
L.R.	Ca Cervix	Negative	Negative	N.E.D.‡(2½ years)
R.G.	Seminoma	Negative	Negative	N.E.D.‡(20 months)
M.W.	Mycosis fungoides	Positive	Positive	Alive, with disease (3 years)
J.W.	N-H L†	Negative	Negative	N.E.D.‡(2½ years)

*For eighteen months or more, following lymphangiography
†Non-Hodgkin's lymphoma
‡N.E.D. = No clinical evidence of disease

TABLE IV

CLINICALLY-FOLLOWED CASES*, IN WHICH THE RADIONUCLIDE STUDY AND THE STANDARD ETHIODOL LYMPHANGIOGRAM WERE IN DISAGREEMENT

Patient	Final diagnosis	Result of radionuclide study	Result of Ethiodol lymphangiogram	Clinical follow-up (length of follow-up period)
R.C.	N-H L§	Positive	Negative	N.E.D.¶(3 years)
S.B.	Dermatomyositis	Positive	Negative	No malignancy (2 years)
G.W.	Ca vagina†	Positive (left pelvis)†	Negative	N.E.D.¶(2 years)
A.F.	Intestinal lymphangiectasia	Negative	Positive‡	No malignancy (18 months)
D.C.	SLE	Negative	Equivocal	No malignancy (2½ years)

*18 months or more, following lymphangiography.

†Had large left-sided pelvic mass at time of lymphography (subsequently treated by irradiation, with clinical regression).

‡Reflux of Ethiodol into mesenteric nodes (not diagnostic of malignancy).

§Non-Hodgkin's lymphoma

¶N.E.D. = No clinical evidence of disease

each other and with the patients' subsequent clinical course (Table III).

Subgroup (4)—In the remaining five patients, on the other hand, the results of the radionuclide study and the standard Ethiodol lymphangiogram differed (Table IV). These five patients, in some of whom the diagnosis had not been established at the time of the lymphangiogram, will be analysed in more detail below with respect to their subsequent clinical course and final diagnosis.

Looking at subgroups 1 to 4 in greater detail, Table I indicates that in 17 of the 24 histologically proven patients, encompassing a variety of primary tumour types, there was perfect agreement between the pathology, the radionuclide perfusion and the Ethiodol examinations. Moving to the second subgroup (Table II), in three of these patients (B.L., M.B., D.M.) the radionuclide perfusion study was positive together with subsequent lymph node histology, whereas the standard Ethiodol lymphangiogram was falsely negative. In two other patients listed in Table II (A.M. and M.P.), the radionuclide and histological examinations were both negative while the Ethiodol lymphangiogram was falsely positive. However, in the remaining two patients listed in Table II (B.W. and R.F.), the radionuclide study was falsely positive in the face of a normal Ethiodol lymphangiogram and normal histological lymph node examination. In one of these patients (B.W.), the radionuclide study and the standard lymphangiogram were performed after recent intensive irradiation of the pelvis (with a good clinical response), the patient having presented initially with a "frozen pelvis from extensive local tumour." Following the lymphangiograms, pelvic exploration in this patient revealed "no viable tumour".

Of the ten patients who have been followed clinically for 18 months or more, the radionuclide perfusion study and Ethiodol lymphangiogram were in complete agreement in five patients (Table III), and subsequent clinical follow-up has corroborated the findings of both studies. Of greater interest are the five patients followed clinically in whom there was disagreement between the results of the radionuclide perfusion study and the Ethiodol lymphangiogram (Table IV). In three of these five patients (S.B., A.F., and D.C.), subsequent clinical and laboratory studies have established that the patients had non-malignant conditions. In two of these patients (A.F. and D.C.), the radionuclide study was correctly negative, whereas the Ethiodol lymphangiogram was interpreted either as equivocal or positive for tumour. In the third patient (S.B.), the radionuclide perfusion study was falsely positive in the face of a subsequent clinical diagnosis of dermatomyositis (the Ethiodol lymphangiogram in this patient was negative). Finally, in the two remaining patients (G.W. and R.C., in Table IV), both patients are now living after treatment without clinical evidence of residual or recurrent tumour two years and three years respectively following their lymphangiograms. In both of these patients, the radionuclide study had been interpreted as "positive" whereas the Ethiodol lymphangiogram was negative for pelvic and periaortic lymph node involvement. Accordingly, for purposes of analysis in these two patients, the radionuclide studies are also regarded now as "false positives" (Table V).

TABLE V

SUMMARY OF COMPARATIVE ACCURACIES OF RADIONUCLIDE PERFUSION STUDIES AND STANDARD ETHIODOL LYMPHANGIOGRAMS IN THIRTY-FOUR PATIENTS

	True positives	False positives	True negatives	False negatives	Totals
Radionuclide perfusion lymphangiogram	11 (32%)	5 (15%)	18 (53%)	0 0(%)	34
Ethiodol lymphangiogram	8 (24%)	4* (12%)	19 (56%)	3 (9%)	34

*Includes one result interpreted as "equivocal" (D.C., in Table IV)

In summary, of 24 patients now available for analysis from 41 studied in our initial series, there is disagreement between the initial radionuclide perfusion study, the standard lymphangiogram, and/or with lymph node histology in 12 patients (Tables II and IV). Of these 12 "discordant" cases, there were none in whom the radionuclide perfusion examination was falsely negative. Indeed, in three of these 12 cases the radionuclide examination was correctly "negative" in the face of a false-positive Ethiodol lymphangiogram (A.M. and M.P. in Table II; A.F. in Table IV). In five of these 12 "discordant" cases (B.W. and R.F. in Table II; R.C., S.B. and G.W. in Table IV), the radionuclide perfusion study did prove to be falsely positive. This represents a false-positive rate for the radionuclide perfusion technique of five patients out of 34 now analysable, or approximately 15%. True and false positive and negative rates for both the radionuclide perfusion studies and the standard Ethiodol lymphangiograms in this preliminary series are summarized in Table V.

DISCUSSION

Continuing follow-up of a preliminary series of patients by both radionuclide perfusion lymphangiography and by standard Ethiodol method has revealed a consistent pattern: in all patients the radionuclide technique has successfully detected pelvic or retroperitoneal lymphadenopathy which was confirmed subsequently on pathological examination (Tables I and II). In ten additional patients in whom clinical follow-up alone is currently available, all six negative radionuclide studies have proved consistent with the patients' subsequent clinical courses (Tables III and IV). Furthermore, in three histologically-proved cases (B.L., M.B. and D.M. in Table II) the radionuclide examination revealed an obstruction to lymph flow which was not evident (or accompanied by any other abnormality) on the Ethiodol lymphangiogram. The radionuclide perfusion study requires about half an hour to perform after cannulation of the lymph vessels, and the results are immediately available. It has been associated with no allergic or other sequelae in 41 patients, and it may be performed safely when there are relative or absolute contra-indications to a standard Ethiodol lymphangiogram (including allergy to iodine, severe lung disease, mediastinal fibrosis, and/or massive lymphatic obstruction), (Abrams, 1968; Fuches, 1962; Koehler, 1968; Threefoot, 1968).

A negative radionuclide study appears to indicate a low likelihood of tumour involving the common femoral, external iliac, common iliac and/or periaortic lymph nodes. The 15% "false-positive" rate for radionuclide perfusion lymphangiograms in this preliminary clinical series (Table V) is reasonable for a screening study: in the individual patient, the radionuclide perfusion results can be evaluated rapidly and a decision can be made immediately by the radiologist, in consultation with the referring clinician, whether or not to perform a standard Ethiodol lymphangiogram using the same pedal lymphatic cannulae. Delay occasioned by the radionuclide examination and any additional discomfort to the patient are minimal, and the decision on whether to perform a standard Ethiodol lymphangiogram (with its possible attendant risks) can be tailored individually to meet each patient's diagnostic and staging requirements.

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Book review

A Guide to Electrical Hazards and Safety Standards. Topic Group Report 24, pp.9 (incl. references) (London, The Hospital Physicists' Association), £1·00.

This is a very useful booklet which serves as an introduction to the main relevant documents concerned with electrical safety standards, *i.e.* Hospital Technical Memorandum No. 8 which refers to National Health Service requirements, and the draft standard of the International Electro-technical Commission dealing with "General requirements for safety of electrical equipment used in medical practice". These documents contain a considerable amount of detail, and report No. 24 is intended to provide a simple explanation of the underlying physiology and an indication of the points of difference between the two documents.

The report is only seven pages long but it achieves its aim. However, it will be more readily comprehended by someone with a knowledge of the field of hazards of electrical equipment because in some of the descriptions of fault conditions only those familiar with the terminology are likely to understand the text. This is a pity because the report should be of interest to a wider readership than staff specifically concerned with electrical safety matters. For example, in section 4.2 headed Electrical Insulation, it is stated that routine installation tests should apply 500 V d.c. between the combined mains conductors (mains switch open and closed) and earth. What is not said is that the main switch refers to that equipment, and not on the wall or bench. The exercise of a little imagination soon enables one to decide which case is referred to, but we are dealing here with a text which may be widely referred to as a quick guide.

A useful table gives recommended maximum values for earth leakage currents in various conditions. The readability of this table could be improved by the addition of vertical lines separating the sections. The leakage currents listed as permissible for a test in which the mains supply is connected to the patient are given as 0.1 mA in the HTM8 document, 0.05 mA in the IEC document for single fault condition and intra-cardiac connections, and 5 mA for the single fault condition and external patient connections. The difference between the HTM8 and the IEC recommendations seem peculiarly large.

In spite of the criticisms already made that the material is not presented in such a way that it can be understood by "non technical" readers, the report is a very useful one and can be recommended for someone who wants an introduction to the subject.

N. RAMSEY.

1978, *British Journal of Radiology*, *51*, 41–45

Expansion of a negative pi-meson peak to cover a range of depths useful for radiotherapy

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Abstract

A peak 7 cm in extent at the 80% isodose level was obtained in the depth damage profile of chromosome aberrations in lymphocytes from blood samples exposed to pi-mesons. The peak to plateau ratio was 1.4 for dicentrics and 1.6 for total aberrations. This was achieved by superimposing beams of 128, 146 and 166 MeV/c as suggested by a simple model and previously published results. It was observed that the effect of the highest momentum pions was over-estimated, resulting in an early gradual fall off with depth and a useful peak 2 cm less than predicted.

In order to irradiate solid tumours with negative pi-mesons (pions) it is desirable that the peak region of the depth profile should extend over the treatment volume. Previous experiments with pions of momentum 160 MeV/c and about 15% momentum spread yielded a biological profile peaking at 14 cm depth in a plastic phantom with a spread at half height above the plateau value of about 3 cm (Lloyd *et al.*, 1975a). Clearly such a peak is too narrow for therapy. The disadvantage may be overcome in various ways. This paper describes the production of an expanded peak by the superimposition of pions having three values of momentum. The resultant profile as determined with an ionization chamber is compared with a profile of biological damage, measured as the yield of chromosome aberrations induced in human lymphocytes.

Materials and Methods

Blood samples

Freshly taken blood from a healthy adult male donor was heparinized and transferred to 35 0.7 ml polypropylene ampoules which were arranged in a staggered pattern along the axis of the pion beam. The ampoules were within the 80% transverse isodose contour and were held in a water bath maintained at 37°C. The distance from the outer face of the front wall of the bath to the mid-point of each ampoule is shown in Table I, column 2. Following irradiation two whole-blood micro-cultures were set up from each ampoule, the cells being stimulated with phytohaemagglutinin and incubated for 48 hours. Coded slides were examined with the light microscope for unstable chromosome aberrations, *i.e.* dicentrics, centric rings and acentrics. All the preparative techniques and the criteria for microscope analysis followed a routine procedure which has been described by Purrott and Lloyd (1972).

Irradiation

The design and layout of the beam line are described elsewhere and have remained unchanged to date (Perry and Hynes, 1971). The three momenta used, 128, 146 and 166 MeV/c, were chosen so that by adjusting the exposure at each an expanded ionization peak of about 10 cm should be produced in the phantom over depths ranging from 8 cm to 17 cm.

The depth-dose measurements were made using a Baldwin-Farmer air equivalent ionization chamber with a volume of 0.2 cm^3 placed at various depths in the water phantom. The readings were normalized to a monitor which was a transmission ionization chamber placed in front of the phantom. The 0.2 cm^3 chamber was calibrated with ^{60}Co γ radiation and a factor of 0.97 was applied to convert from roentgens to rads in water. No corrections were made specifically for pions. Such corrections would be less than 10% and are discussed by Nias *et al.*, 1974. The depth-dose profiles measured by ionization are shown in Fig. 1.

A previous experiment (Lloyd *et al.*, 1975a) using the same cytogenetic system at one momentum setting of 160 MeV/c had shown a peak to plateau ratio of biological effect about 1.7 times the ratio of doses. In this paper we refer to this as the biological enhancement factor; it is shown in Table II, column 4, where the dose effect data up to 250 rad have been approximated to a linear fit. The model chosen to merge the three momenta settings in the present work assumed that the factor of 1.7 is appropriate for each and the expected distributions of the biological enhancement around the three peaks are shown in Fig. 1.

A matrix was made using the values of the biological depth profiles at the three depths corresponding to the peak of each setting and the exposures

TABLE I

Chromosome aberration yields obtained from blood samples irradiated at various depths in the pion beam

Sample no.	Mid-line depth (cm)	No. cells scored	Dicentrics	Centric rings	Acentrics
1	1.0	496	93	5	38
2	2.8	200	30	1	13
3	3.4	211	32	3	14
4	4.0	155	23	2	10
5	4.6	355	55	3	32
6	5.2	300	50	0	17
7	5.8	470	85	6	41
8	6.4	270	57	2	31
9	7.0	298	50	1	31
10	7.6	240	52	3	24
11	8.2	210	41	1	19
12	8.8	254	55	0	42
13	9.4	240	50	4	35
14	10.0	189	41	1	23
15	10.6	360	76	3	43
16	11.2	410	95	3	69
17	11.8	300	61	2	54
18	12.4	210	50	3	32
19	13.0	210	55	1	34
20	13.6	240	50	2	31
21	14.2	80	16	2	9
22	14.8		Cultures failed		
23	15.4	440	72	1	48
24	16.0	257	44	3	22
25	16.6	360	51	4	44
26	17.2	360	52	2	45
27	17.8	530	74	2	68
28	18.4	260	26	0	26
29	19.0	360	50	3	24
30	19.6	480	51	5	36
31	20.2	94	10	0	6
32	20.8	800	68	2	52
33	21.4	265	18	0	18
34	22.0	750	52	1	35
35	24.0	500	6	2	2

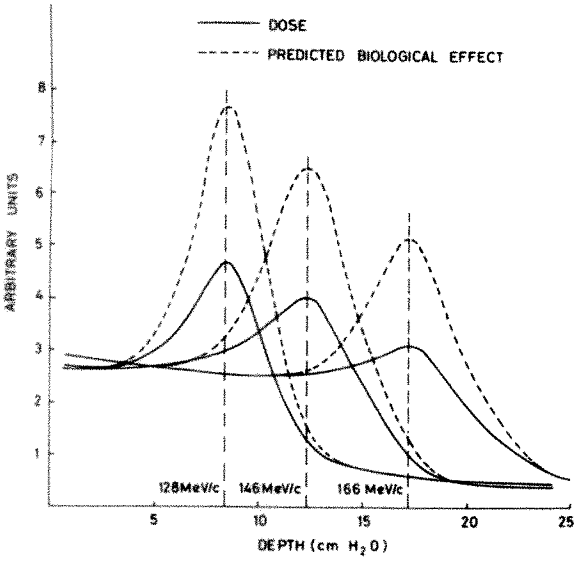

Fig. 1.

Relative dose and assumed biological profiles for the three pion momenta.

needed to produce an equal biological effect at each were calculated. The momenta settings at 128, 146, 166 MeV/c were used in the ratio 0.27, 0.46, 1.0 measured in terms of the monitor. The resultant predicted biological effect and dose profiles are as shown in Fig. 2.

A total of 150 rad was given as this would be a likely daily treatment dose for radiotherapy. This dose was given at 12.4 cm, approximately in the middle of the broad peak produced by the three momenta. During the irradiation three doses of 50 rad were given in three cycles of the three momenta in order to provide a more even dose distribution during the run.

Results and Discussion

The observed chromosome damage is given in Table I and the data for the dicentric yields and for total aberration yields are shown in Figs. 3 and 4, respectively. As well as the predicted curves, Figs. 3 and 4 show how different biological enhancement

TABLE II

ABERRATION YIELDS PER CELL PER RAD OBTAINED FROM A LINEAR FIT TO PREVIOUSLY PUBLISHED DOSE RESPONSE DATA (LLOYD ET AL., 1975a)

	Plateau	Peak	Peak to plateau ratio of yield/rad (biological enhancement factor)
Dicentrics	0.00100 ± 0.00007	0.00167 ± 0,00012	1.67 ± 0.17
Total aberrations	0.00184 ± 0.00012	0.00306 ± 0.00020	1.66 ± 0.15

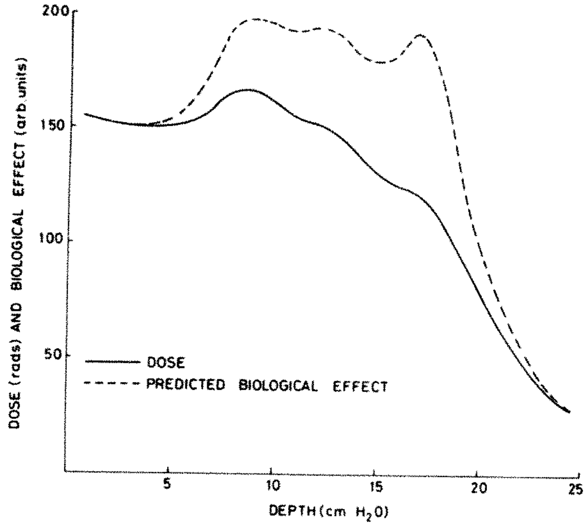

FIG. 2.
The profiles of the three combined momenta.

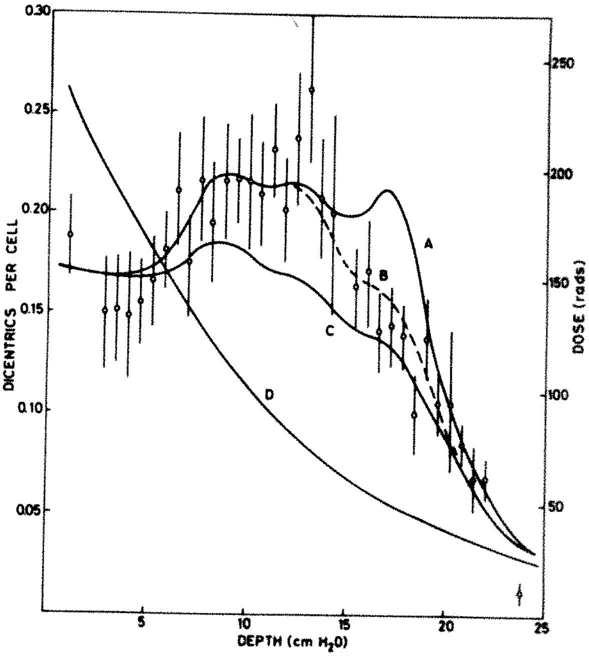

FIG. 3.
Observed yield of dicentric aberrations, prediction using a 1.7 enhancement factor for each momentum (A), using 1.2 for 166 MeV/c (B), and the pion dose profile (C). Also shown is a damage profile for 150 rad ^{60}Co γ radiation at 12.4 cm depth (D).

factors would improve the fit (dashed lines). The dicentric data (Fig. 3) agree with the prediction except for a fall-off at the position corresponding to the peak of the highest momentum. Here the dashed line is drawn for an enhancement factor of 1.2. In view of the similarity between the highest momentum, 166 MeV/c, and that used in the previous experiment, 160 MeV/c, the low aberration yields observed in samples at depths of 15–18 cm were unexpected and cannot be explained from physical considerations. A replicate exposure was made and a few selected blood samples analysed. At depths of 16 and 17.8 cm low aberration yields were again obtained, 0.17 and 0.12 dicentrics per cell respectively. If further work confirms this effect it would be important for radiotherapy.

The data for total aberrations (Fig. 4) show a similar fall-off. There is an indication of an increased enhancement for the middle momentum for both end points. The dashed curve on Fig. 4 is for the case of a plateau yield 14% lower than the best previous determination, *i.e.* 0.00158 aberrations per cell per rad and biological enhancement factors of 2.4, 2.8 and 1.5 for 124, 146 and 166 MeV/c respectively. A similar re-normalized curve would also fit the dicentric data.

The ratio of observed damage between the highest point in the peak (12 cm) and the lowest in the plateau (3 cm) is about 1.5 for dicentrics and about 1.8 for the total aberrations. Taking average values across the peak (7–14 cm) and the plateau (1–5 cm), the ratios are about 1.4 and 1.6. All are slightly more favourable than the ratio for the predicted profile, 1.3. Nevertheless, as expected, they are significantly less than the value of 2.6 found by Lloyd *et al.* (1975a) with the single momentum setting.

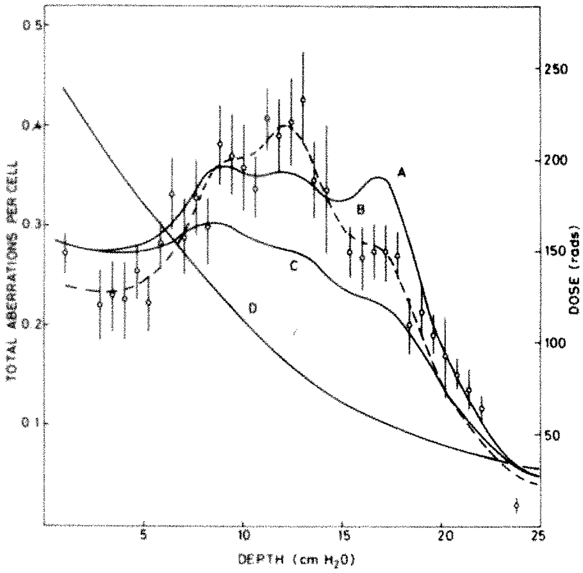

FIG. 4.

Observed yield of total aberrations, prediction using a 1.7 enhancement factor for each momentum (A), taking a 14% lower yield at the plateau and enhancements of 2.4, 2.8 and 1.5 for the three momenta (B), the pion dose profile (C), and a ^{60}Co γ aberration profile (D).

A calculation of how the enhancement factors may be expected to vary has been made by considering the ratio of the high LET component from pion absorption to the low LET component from beam particles in flight. Taking parameters appropriate to this beam, and assigning an RBE of 3.0 to the high LET component, enhancement factors of 1.63, 1.59 and 1.53 were found for the three settings. These values are close to those given in Table II, column 4, and are not sufficient to account for the variations found, especially for the total aberrations.

Similar calculations by Li *et al.* (1974), starting from theoretical depth-dose curves for small momentum bites, produced a depth profile to deliver a uniform effect in a 10 cm cube tumour. The profile has a significantly higher peak than ours. This is because our beam is more subject to losses by scattering due to its small cross-sectional area (4.5 cm full width at half-height), its divergence (0.85% per cm) and a large momentum bite (13% full width at half-height). These features result in a low peak-to-plateau ratio for the 166 MeV/c setting which cannot be regained by the smaller additions of the two lower momentum components. The calculated enhancement factors however do agree in the central region of the peak for there the quality of the radiation is not significantly affected by the differences in the beam parameters.

At the position of the first blood sample, 1 cm deep into the plateau, a high aberration yield was observed relative to the subsequent five samples. This phenomenon has also been described with two other biological systems, namely by Winston *et al.* (1974) who studied the inhibition of bean root growth, and by Nias (1976) who examined the survival of frozen HeLa cells. The final position in the tail (24 cm) gives a very low yield consistent with an RBE of 1.0 and well below the plateau value of 1.5. Physical and biological experiments are being prepared by this group to study the front of the plateau in detail and the enhancement factors at each momentum setting separately over the peak and in the tail.

For comparison with conventional depth-dose curves, the profile of biological damage in terms of aberration yields for ^{60}Co γ-radiation in a unit density material is also shown in Figs. 3 and 4. The curves were obtained from the depth dose data for a 20×20 cm field at 100 cm SSD (Kemp and Cohen, 1961) and the data were converted into aberration yields for ^{60}Co delivered at 18 rad per hour (Lloyd *et al.*, 1975b) for a dose of 150 rad at 12.4 cm depth.

Several theoretical attempts have been made to assess the effects of widening of the peak (Li *et al.*, 1974; Armstrong *et al.*, 1973). However, the work reported here is the first to give experimental results with a biological system for the combination of pion beams of different momenta. It has been observed that radiobiological experiments with pions are only clinically relevant when they are conducted under the same conditions as are likely to be used with patients (Fritz-Niggli, 1976). While this is clearly correct, at this early stage in the development of pion radiotherapy experimental work of the type presented here is necessary to assist the therapist to determine the optimum application of pion beams.

CONCLUSIONS

For pion radiotherapy the ionization peak needs to be enlarged and the work reported here based on radiation-induced chromosome aberrations in human lymphocytes has demonstrated that this may be achieved by using a beam in which several pion momenta are combined. A 7 cm extended peak region was obtained by the superimposition of three momenta settings of the Rutherford Laboratory's pion beam line. The peak to plateau ratios were 1.4 for dicentrics and 1.6 for total aberrations. In both cases the biological effect in the peak region was greatest for 146 MeV/c and significantly lower at 166 MeV/c. Therefore it is clear that the present method of widening the pion peak must be preceded by a more detailed study of likely momenta, examined separately, to determine the relationship between dose and biological effect at varying depths, especially across the peaks.

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A search for an effect of ultrasound alone and in combination with X rays on chromosomes *in vivo*

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ABSTRACT

Experiments were aimed to establish whether therapeutic doses of ultrasound are liable to cause demonstrable chromosomal damage in marrow cells of the mouse. On evaluation of the chromosome aberrations no significant increase was found after treatment with three different doses of ultrasound. In contrast, our "positive control group" irradiated with 50 R of X rays showed clearly demonstrable chromosomal damage. In another group of animals treated with ultrasound plus X rays, the ultrasonic pretreatment did not increase the damaging effect of X rays significantly.

The widespread medical application of ultrasound can be attributed to the fact that it is a non-ionizing radiation which can be considered harmless for genetic material. Several experiments have been carried out since 1970 that justify this statement. The biological effects of ultrasound depend primarily on the applied frequency, intensity and duration of exposure. The most important factor amongst these physical parameters is intensity which is about a hundred times higher in therapy than in diagnosis.

The genetic effect of ultrasound has been investigated extensively by insonication of human peripheral blood and tissue cultures *in vitro*. The results of these experiments have been generally negative (Abdulla *et al.*, 1971; Coakley and Slade, 1971; Buckton and Baker, 1972; Mackintosh *et al.*, 1975; Watts *et al.*, 1972).

The results of the recent DNA studies reported by Galperin-Lemaitre *et al.* (1975, 1976) deserve attention. Insonication *in vitro* of purified DNA at an intensity only ten fold higher than the diagnostic dose (200 mW/cm^2) produced electron-microscopically demonstrable DNA breakages.

After treatment of HeLa tissue cultures with diagnostic doses of ultrasound, a 14% decrease in DNA synthesis has been found by investigation with ^{3}H-thymidine (Prasad *et al.*, 1976.). These observations are not, of course, applicable to normal tissue conditions; thus they imply the necessity of further studies *in vivo*.

Our experiments were aimed at determining whether therapeutic doses of ultrasound produce demonstrable chromosome abnormalities under *in vivo* conditions. Laboratory mice were insonicated from a therapeutic equipment and bone marrow cells were prepared for demonstration of resulting chromosome damage. Apart from the untreated control group, we have also used a so called "positive control" irradiated with X rays. Our aim was to find out whether if a known mutagenic agent, in our case X rays, is applied in combination with ultrasound they are affected by each other. The chromosome preparation was made 24 hours following insonication and irradiation with X rays. Combined treatment of somatic chromosomes was investigated in order to determine whether insonication increased the mutagenic effect of X rays.

MATERIALS AND METHODS

Our experiments were carried out on eight-week-old male CBA/H–T$_6$J mice of 23–25g body weight. Experiments in radiation genetics appear to justify the assumption that reactions obtained in mice represent a good approach to human conditions though evaluation of chromosomes of the golden hamster and the rat present fewer difficulties.

The animals were divided into the following seven groups.

Group A

The animals received the same treatment as their test counterparts, but without exposure to ultrasound or X rays (ten mice).

Groups B–C–D

The animals were insonicated with three different doses of ultrasound: 0.1, 0.5 and 1.0 W/cm^2 (spatial average intensities; six mice per group).

Group E

The animals were treated with 50 R whole body X ray irradiation, "positive control group" (six mice).

Groups F–G

Combined ultrasound and X rays were applied. Both groups received the same irradiation of 50 R but the intensity of ultrasound was different: 0.1

and 1.0 W/cm^2 (five mice per group). The X rays were applied two hours after ultrasonic treatment.

The ultrasonic waves were generated from Ultron T-11 type therapeutic apparatus working at 800 kHz, set for continuous emission. The diameter of the probe was 2 cm. The intensity was measured on the therapeutic equipment as the output level. Exposure time was the same in each group, *i.e.* five minutes. Some minutes prior to insonication the animals were anaesthetized by i.p. Nembutal (30mg/kg). The animals, fixed by the extremities, were submerged in the coupling medium up to the abdomen to ensure good acoustic coupling between the transducer and the shaved skin of the animal. For the X-ray treatment, a Stabilipan (Siemens) apparatus was applied to deliver 50 R whole body irradiation (190 kV, 20 mA, 20.7 R/min, Al filter of 4 mm, measured HVL 0.56 mm Cu).

The mice were killed 24 hours after insonication or irradiation and chromosome examination was made by Ford's method directly from the bone marrow. In all probability the cells received the exposure in G_0 and went through a single cell division. The cells flushed out from the femur were placed in a Tc-199 solution and incubated, after addition of colchicin, at 37°C for two hours. Following centrifugation the sedimented cells were submitted to hypotonic shock in 0.075 M potassium chloride solution for 25 minutes and then again centrifugated and fixed three times in 1:3 acetic acid–methanol solution. The cell suspension obtained was dropped onto a cleaned slide and dried in air. The preparation was stained with Giemsa solution.

Chromosome aberrations were assessed partly microscopically and partly on the basis of microphotographs. Scoring of aberrations was carried out "blind". A total of 2150 metaphases were evaluated in the seven groups. Statistical analysis was performed by χ^2 test. The normal mouse karyotype is characterized by 40 acrocentric chromosomes classified according to size. At evaluation the following aberrations were taken into consideration—structural aberrations: acentric fragments, chromatid and chromosome deletions, metacentric chromosomes, ring chromosomes; numerical aberrations: hypodiploid cells (number of chromosomes less than 40), and polyploid cells (these were always tetraploid in our material).

RESULTS

The structural and numerical aberrations observed in the ultrasound, X-ray, and ultrasound plus X-ray treated groups, as well as the untreated controls, are indicated in Table I. The structural aberrations of the three ultrasound treated groups showed no significant increase as compared with the untreated control. Increase in intensity did not lead to a proportionate increase in the quantity of structural aberrations. In contrast, the number of aberrations was significant after irradiation with X rays as compared with both the untreated control and the ultrasound treated groups ($p < 0.05$). As compared with the controls, a significant difference is obtained

TABLE I

CHROMOSOME ABERRATIONS PRODUCED BY ULTRASOUND AND X RAYS

	Control	Ultrasound			50 R X rays	50 R X rays plus US	
		0.1 W/cm^2	0.5 W/cm^2	1.0 W/cm^2		0.1 W/cm^2	1.0 W/cm^2
Total cells scored	600	250	250	250	300	250	250
Total structural aberrations, %	1.83	3.2	4.0	3.6	10.66	12.4	8.0
Metacentrics	1.16	2.4	2.0	1.2	4.66	4.0	1.2
Acentrics	0.5	0.4	1.6	0.4	5.33	6.4	2.4
Rings	—	—	—	0.4	—	0.4	—
Chromatid deletions	0·16	0.4	0.4	1.2	0.66	1.6	4.0
Chromosome deletions	—	—	—	0.4	—	—	0.4
Structural aberrations per cell	1.0	1.33	0.81	1.0	1.45	1.45	1.11
Total numerical aberrations, %	5.66	4.4	6.0	5.6	9.33	5.2	6.0
Hypodiploid	3.83	2.4	4.4	4.8	7.33	4.0	4.4
Hyperdiploid	1.83	2.0	1.6	0.8	2.0	1.2	1.6

in our statistical test if more than 4% of the treated cells showed structural aberrations.

The second question was whether ultrasonic pretreatment enhanced the damaging effect of X rays. At the doses applied by us, no significant difference was observed between the X-ray treated groups and the ones exposed to ultrasound and X rays. Our experience suggests that low doses of ultrasound do not influence synergistically the chromosome damage produced by X rays.

DISCUSSION

Exact determination of the intensity of ultrasound at the bone marrow cells is difficult. The ultrasonic energy reaching the medullary cavity depends on several factors: sound absorption of the layers above the bone, and scattering and reflection of sound before it reaches the cells. In calculating the effective dose, reflection from the muscle-bone boundary and absorption of the soft tissues and the bone were taken into consideration (Fry and Dunn, 1962; Farkas and Irányi, 1965). Thus the ultrasound intensities reaching the medullary cavity in our case were estimated to be: 0.055 W/cm^2 (at 0.1 W/cm^2); 0.368 W/cm^2 (at 0.5 W/cm^2); and 0.736 W/cm^2 (at 1.0 W/cm^2).

In accordance with published data our results confirm the harmlessness of diagnostic doses of ultrasound. The demonstration of the absence of any genetic damage caused by diagnostic ultrasound is one of the basic arguments justifying its increasing application in diagnosis.

Absence of mutation has been observed in a bacterial test following insonication (Combes, 1975). The conventional subject of genetic experiments, *Drosophila melanogaster*, was severely affected only after long exposure to high doses of ultrasound (Thacker and Baker, 1976). Levi *et al.* (1974) investigated somatic chromosomes of the golden hamster after insonication with therapeutic doses. In agreement with our observations they did not notice any significant increase in the rate of aberrations. Testes and ovaries of mice were exposed to continuous and pulsed ultrasound by Lyon and Simpson (1974). No significant damage to the gonads was observed.

It should be emphasized that no paper is known which reports genetic damage in humans caused by diagnostic doses of ultrasound. In chromosomes harvested from insonicated lymphocytes of fetuses and their mothers no significant increase of abberations was detected (Abdulla *et al.*, 1971; Korányi *et al.*, 1972). Cytogenetic preparation of human fetuses exposed to ultrasound prior to artificial abortion also failed to reveal aberrations (Ikeuchi *et al.*, 1973). The studies cited include, of course, only microscopically detectable damage, but the possibility of point mutations can still not be excluded. We have not found that ultrasound increases the number of chromosome aberrations produced by X rays in the doses we have used. This observation is in close accord with a problem investigated earlier which has recently been raised again in connection with the combined application of ultrasound and X rays in the treatment of tumours. Favourable results were obtained in the treatment of both animal tumours and certain human neoplasms (Horváth, 1946, 1948; Woeber, 1951). Ultrasound by itself fails to destroy tumours at a satisfactory rate and selectivity, but at an intensity of several W/cm^2 its damaging effect on the tumour is added to that of X rays. The biological mechanism of action of the combined treatment and the possibility of its clinical use have come into prominance again (Fleisher, 1975; Heimburger *et al.*, 1975). The absorbed ultrasonic energy is almost completely converted into heat and the synergistic effect between ultrasound and X rays can be explained by localized temperature rise and improved oxygenation, due to local vasodilatation caused by ultrasound. Kunze-Mühl (1975) reported results obtained with a combination of ultrasound and X rays on human peripheral blood *in vitro*. The aberration rate caused by high dose ultrasonic pretreatment was not significantly higher than that brought about by irradiation with X rays alone. The insonication of X-ray damaged cells increased the aberration rate significantly. The application of low intensity ultrasound prior to irradiation with X rays induced only a distinct rise in the number of aberrations, whereas this value was significantly lower in the case where insonication followed irradiation, as compared to X ray control values. Our ultrasound intensities were between the ones applied in their experiment: neither 0.1 nor 1.0 W/cm^2 insonication resulted in a significant rise of aberrations.

Regarding the results of the above-mentioned studies of DNA and exposures of tissue cultures we should be cautious, since the theoretical possibility that ultrasound alone or in synergism with other mutagenic effects may cause DNA damage cannot be ruled out. This calls for further *in vivo* studies to determine the limiting intensities that are regarded as harmless in relation to humans. The findings will also depend on the sensitivity of the methods used: the application of banding techniques is expected to provide more information. We suspect that ultrasound is a harmless procedure in diagnostic practice although genetic investigations must be continued until we know the "safe" ultrasound levels.

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Technical notes

A new gamma camera method for the measurement of thyroid uptake of technetium 99m pertechnetate

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Measurement of the early thyroid uptake of ^{99}Tc^{m} pertechnetate complements biochemical thyroid function tests by providing an index of thyroid "trapping". This is not affected by commonly used antithyroid drugs so the technetium uptake performed during antithyroid drug therapy is used to follow progress of the underlying thyrotoxicosis. In addition, discordance between the thyroid technetium uptake and serum thyroxine level identifies cases of thyroiditis or organification defects (Marion *et al.*, 1974). We describe a method of measuring thyroid technetium uptake with a gamma camera and region-of-interest modification, which gives reliable results.

Although Atkins and Richards (1968) measured thyroid ^{99}Tc^{m} uptake with a modification of the probe system used for ^{131}I thyroid uptake, subsequent workers used quantitative rectilinear scans (Shimmins *et al.*, 1968; Williams *et al.*, 1972). More recently others have used a gamma camera, usually with a computer or multichannel analyser (Hurley *et al.*, 1972; Armstrong *et al.*, 1975; Cauwe *et al.*, 1976). Marion *et al.* (1974) using a gamma camera relied on a short pinhole-to-surface distance to exclude most non-thyroidal neck activity. This method introduces problems with respect to reproducibility owing to the pronounced effect of distance and thyroid size on the detector response. Wilson *et al.* (1975) used an electronic region-of-interest selector as well as a pinhole collimator, and by calculation from a lateral view corrected for attenuation but not for variation in pinhole-to-surface distance. Thyroid uptake studies with pertechnetate were performed on patients referred to this department for thyroid investigations. About 186 MBq (5 mCi) of ^{99}Tc^{m} – sodium pertechnetate was injected intravenously. A Pho Gamma III (Searle radiographics) gamma camera with a low energy parallel hole collimator was fitted with an electronic region-of-interest attachment constructed in the department. This was used to define a rectangular region of interest encompassing the thyroid. Fifteen minutes after injection the count rate in the region of interest was recorded from a ratemeter using a ten-second time constant. Within five minutes a ratemeter reading was taken from a reference consisting of 10% of the injected dose in a standard Lucite ORINS neck phantom (Brucer, 1959) at the same collimator-to-surface distance, usually 7 to 10 cm. If necessary the size of the region of interest was increased to encompass the standard source. No attempt was made to subtract extra-thyroidal neck activity.

Electronic region-of-interest selectors are readily available, if not standard or optional features of most modern gamma cameras, whereas on-line computers are less generally available. To overcome the problem of region-of-interest selection without a computer, Marion *et al.* (1974) used a pinhole collimator with a short skin-to-collimator distance. This introduces a large error with minor variations in distance (Fig. 1). Armstrong *et al.* (1975) and Hurley

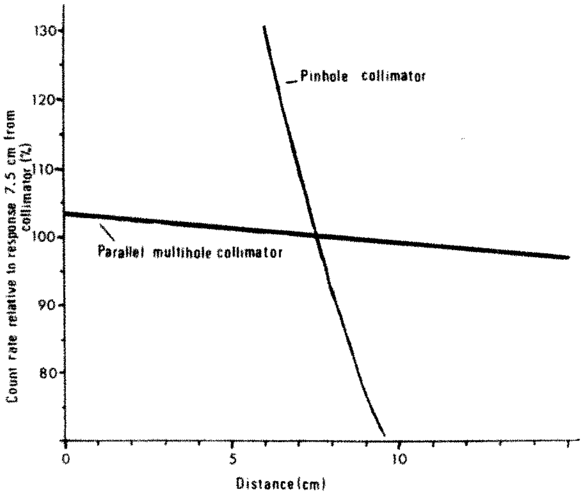

Fig. 1.

Relative sensitivity of gamma camera to activity in a thyroid phantom at varying distances, using a pinhole or parallel multi-hole collimator.

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TABLE I

FIFTEEN-MINUTE ^{99}Tc^{m} THYROID UPTAKE

	Diagnosis by independent criteria Hypothyroid	Euthyroid	Hyperthyroid
Number	9	27	18
Mean uptake (%)	0.9	2.2	9.9
Standard deviation	0.52	0.68	6.5

Euthyroid 68% confidence limits 1.5–2.8
Euthyroid 95% confidence limits 0.8–3.5

et al. (1972) have shown that it also causes diminishing sensitivity to a uniform plane source towards the periphery of the camera field which requires a further correction. Failure to do this could be a factor in the low or normal thyroid ^{99}Tc^{m} uptakes observed by Marion *et al.* (1974) in large toxic multinodular goitres.

Armstrong *et al.* (1975) showed that calculating background from adjacent areas of the neck gave, if anything, less accurate results than subtracting a constant fraction of the dose. Elimination of this step should therefore merely give a correspondingly higher normal range. Use of the parallel-hole collimator with a region-of-interest selector markedly reduces instrument-related sources of error in measuring thyroid ^{99}Tc^{m} uptake, and in our experience provides a convenient reliable system for routine thyroid assessment. Table I gives our results for the uptake of ^{99}Tc^{m} at 15 minutes in hypothyroid, euthyroid and hyperthyroid patients.

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A technique for measuring the accumulation of ^{99}Tc^{m} stannous-ethane-1-hydroxy-1, 1-diphosphonate in the canine tibia

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ABSTRACT

An experimental technique is described to measure the accumulation of ^{99}Tc^{m}-stannous-ethane-1-hydroxy-1, 1-diphosphonate (^{99}Tc^{m}-EHDP) in the canine tibia. The method involves infusion at a constant rate of known amounts of ^{99}Tc^{m}-EHDP into the nutrient artery supplying the tibial bone. The accumulation of the diphosphonate in bone is measured by an external sodium iodide, NaI (Tl), scintillation detector. Results are presented showing that for small amounts of ^{99}Tc^{m}-EHDP (0.004–0.300 mg per hour) the accumulation is a nearly linear function with time for 60 minutes, after which the uptake may become variable with either a plateau formation or considerable fluctuation of activity.

A number of studies have been made concerning the relationship between blood flow and bone uptake of a bone-seeking radionuclide, Copp and Shim (1965), Van Dyke *et al.* (1965), Kane (1968), Wootton (1974), Tothill and McCormick (1975) and Hughes *et al.* (1977). Standard methods of estimating bone blood

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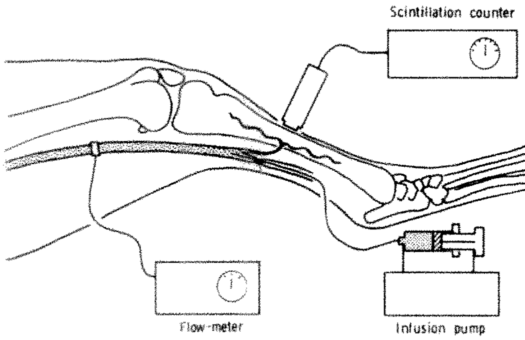

FIG. 1.

Diagram of the experimental model showing the hind leg of the dog with the electromagnetic flow probe around the femoral artery, the catheter which has been passed retrogradely into the anterior tibial artery and attached to the infusion pump, and the scintillation counter over the infused tibia.

flow may use measurements of blood concentrations of the tracer, a determination of the bone tracer uptake per unit mass, and the assumption of 100% tracer extraction or the use of an extraction ratio. Such extraction ratios, *i.e.* the amount extracted at one passage through bone or over short intervals of time have been determined for a number of nuclides including ^{85}Sr, ^{18}F and $^{99}\mathrm{Tc^m}$-labelled phosphate compounds.

The present technique using an infusion at a constant rate of known amounts of $^{99}\mathrm{Tc^m}$-EHDP into the tibial nutrient artery allows the inflow of this agent to be studied over relatively long time periods.

MATERIALS AND METHODS

Experimental procedure

A diagram of the experimental model is shown in Fig. 1. Nine greyhound dogs weighing between 21 and 35 kg were anaesthetized with intravenous thiopentone and pentobarbitone sodium (30 mg per kg). Endotracheal intubation was carried out and the dogs kept warm throughout the experimental period.

An antero-lateral approach was used to expose, isolate and retrogradely cannulate the anterior tibial artery using polyethylene tubing (internal diameter of 0.58 mm). The nutrient artery to the tibia arises as a branch from the anterior tibial artery at a point about 7 cm inferior to the joint space of the knee, on the lateral aspect of the tibia and anterior to the interosseous membrane. From this point it runs close to the lateral and posterior surfaces applied to the tibial periosteum and enters the nutrient foramen which runs obliquely in the cortex.

The catheter was advanced so that its tip lay at the origin of the nutrient artery and the ligature was tied a little below this point. The position of the tip of the catheter was checked by fine detail angiography using a slow infusion of contrast medium. A careful inspection was made for intramuscular branches around the region of the nutrient artery and these were tied off at their points of origin from the anterior tibial artery (Fig. 2). Initially femoral blood flow was monitored in five dogs using an electromagnetic flow probe and this remained constant during the experimental period.

$^{99}\mathrm{Tc^m}$-*EHDP infusate*

The infusate was prepared by addition of 5 ml free $^{99}\mathrm{Tc^m}$-pertechnetate solution, eluted from a ^{99}Mo column and containing the required amount of radioactivity, to a mixture of 5 mg EHDP and 1 mg $SnCl_2.2H_2O$. The mixture was agitated vigorously for two minutes to ensure complete and uniform labelling and a further 100-fold dilution in normal saline was carried out prior to start of infusion. The effect of 1 : 100-fold dilution on the stability of the preparation was pre-tested in rabbits, and no significant difference in bone uptake was found even after storage of the preparation at room temperature for two hours before injection. The amounts of EHDP ranged from 0.004 to 0.300 mg per hour and this was delivered by a constant rate infusion pump over a period varying from one to five hours. The total volumes of infusate ranged from 2 to 10 ml. The amounts of EHDP used are comparable to that which would be deposited in a tibia during a clinical study—estimated at 0.25 mg.

External counting

The basic counting equipment consisted of a 4.5 cm × 5 cm NaI(Tl) crystal scintillation detector, the output of which was fed to a scaler-ratemeter unit. The detector was clamped in an adjustable, counterbalanced holder and placed in contact with the tibial bone. The straight bore collimator with 1.5 cm thick lead walls had an aperture of 5 cm and extended a distance of 11.5 cm from the face of the crystal.

$^{99}\mathrm{Tc^m}$-EHDP was administered as a continuous infusion and the fluctuations of radioactivity in the field "seen" by the detector were recorded as a function of time.

Soft tissue and recirculation corrections

A small proportion of the pulses recorded at each measurement was due to plasma and soft tissue lying in the field of view of the detector. The

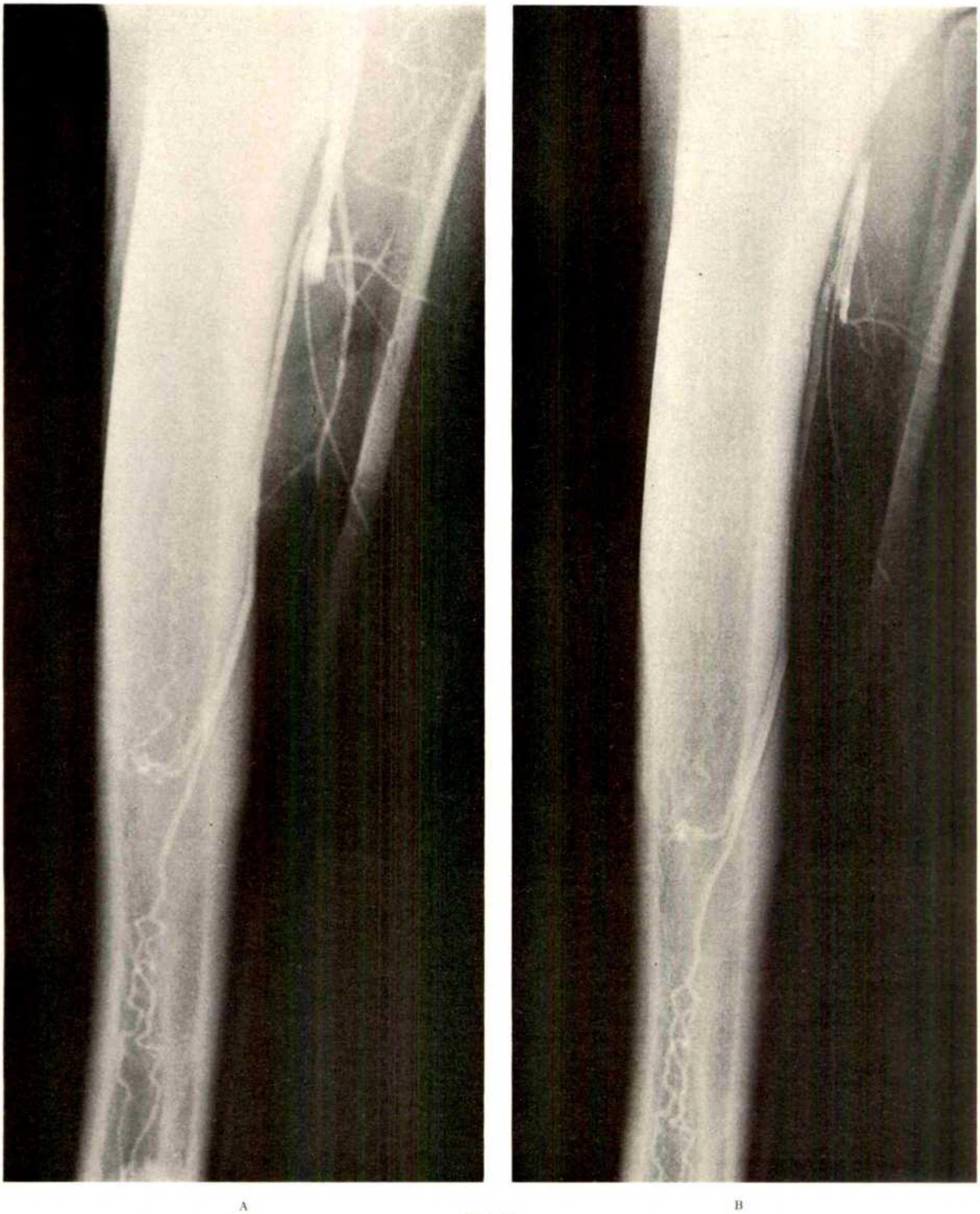

FIG. 2.

(A) Bolus injection of radiographic contrast showing filling of the tibial nutrient artery, muscular branches and retrograde filling of the anterior tibial artery.

(B) Trickle injection of radiographic contrast showing filling of the nutrient artery and a muscular branch of anterior tibial artery.

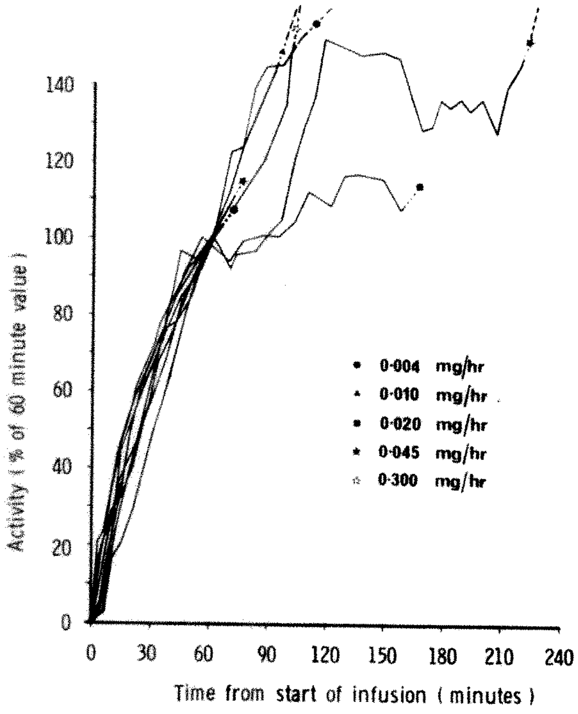

Fig. 3.

Graphs showing the accumulation of ^{99}Tc^{m}-EHDP expressed as a percentage of the 60-minute value against time.

contribution was estimated at the end of infusion by taking a blood sample and probe measurement both before and at 5 min. after injection of ^{99}Tc^{m}-pertechnetate thus causing a known change in plasma levels. The change in probe measurements over the tibial region ranged from 1 to 3% and this correction was applied to the appropriate time-activity curve.

The contribution from recirculating ^{99}Tc^{m}-EHDP was assessed by measuring the activity over a corresponding region of the non-cannulated contralateral tibia at the end of the infusion period. The same probe and a similar geometry was used as for the infused tibia. The activity was invariably found to be less than 1% that of the infused bone.

Results

In all nine experiments with selective infusion into the nutrient artery the activity in bone increased, commencing as a linear function, but in the majority of experiments showing some diminution of the extraction rates during the latter part of the 60 minute period (Fig. 3). Beyond 60 minutes the behaviour of ^{99}Tc^{m}-EHDP accumulated in the bone varied in some experiments showing either a plateau

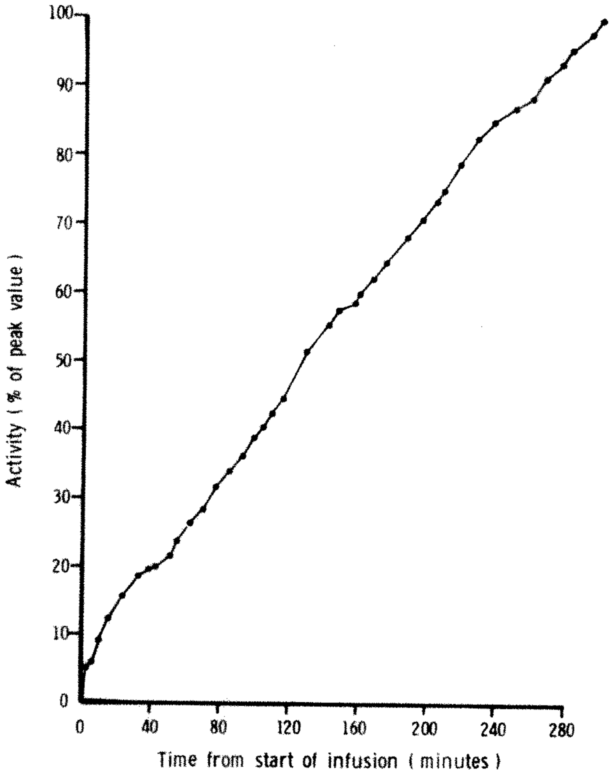

Fig. 4.

Graph of one experiment showing the accumulation of ^{99}Tc^{m} EHDP in the dog tibia over a period of five hours.

formation or considerable fluctuations in activity. In one experiment, however, the linear extraction was maintained for five hours (Fig. 4).

Discussion

The purpose of this paper is to present a simple technique which allows selective infusion of known amounts of bone seeking radionuclide into the tibial nutrient artery of the dog. The procedure of isolating the nutrient artery is not new having been used by a number of workers. The method of retrograde cannulation described here has the advantage of maintaining normal nutrient flow to the bone. This therefore allows a study of changing levels of bone seeking radionuclides over relatively long intervals of time in contrast to previous studies in which extraction ratios have been determined following bolus or short infusions and this may have a relevance to studies in patients undergoing bone scanning.

The data presented suggests that under the presumed stable conditions of bone blood flow, extraction remains approximately linear for 60 minutes, slight diminution in the ratio being seen during the latter part of this time. Beyond this point, inflow may show either plateau formation or become erratic. This latter behaviour was not dose dependent within the limits used, and therefore does not appear to be a saturation phenomenon. However, it is possible that much larger amounts of EHDP might indeed show this phenomenon. It may of course reflect a biological deterioration in the preparation although this seems unlikely, and no evidence for this was observed at the time. Again time related chemical changes in ^{99}Tc^{m}-EHDP complexes seem improbable due to variations in time between the preparation of the radiopharmaceutical to the observed plateau effect.

A hypothesis could be offered to explain these observations of a tissue-space of limited capacity which might be "filled"; that is, the inflow concentration and tissue-space concentration equalize. This equilibrium may be unstable and result in fluctuations of tracer level observed. Such a hypothesis would mean that the initial extraction ratio of tracer and the accumulation of tracer in bone are not necessarily the same rate controlled processes.

ACKNOWLEDGMENTS

We wish to thank Dr. M. Myers and Miss R. Arnot for their generous help, and Miss L. Draper for typing the manuscript.

Ralph A. Khan was supported by a grant from the Cancer Research Campaign.

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Case report

Ultrasonic diagnosis of haematocervix following cone biopsy of the cervix

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Haematocervix is a rare condition in which the cervix is dilated and the endocervical canal is filled with blood. Jeffcoate (1967) described a case of haematocervix in a patient with vaginal atresia. Clark *et al.* (1973) described two cases of haematocervix following cone biopsy and dealt with by total abdominal hysterectomy. Recently one case following cone biopsy has been seen in our hospital, diagnosed with ultrasonography. This to our knowledge is the only one reported in the literature.

CASE REPORT

A para II patient, aged 30, had knife cone biopsy of the cervix in January, 1976 for carcinoma *in situ*, diagnosed during routine cervical cytological examination. Four haemostatic sutures were applied to the cervix. No curettings were obtained and the histology report showed carcinoma *in situ* with no glandular penetration or stromal invasion.

Post-operative condition was uneventful and the patient was discharged home with an appointment for out-patient cytological follow ups.

In the following six months, she was seen on four occasions in the out-patients department. Cervical cytological examinations were negative, but the patient mentioned that she never had a period. Vaginal examinations showed no abnormalities and two pregnancy tests were negative.

In October, 1976 she was admitted as an emergency with lower abdominal pain, backache and vomiting of ten days duration. There was tenderness in the hypogastrium and on vaginal examination the cervix was found healthy and the os was closed. The uterus was enlarged, corresponding to eight to ten weeks of pregnancy. Both ovaries were normal. Haematological and biochemical investigations were normal. Pregnancy test was negative.

At this stage we were asked to perform an exploratory ultrasonic scanning examination, and we found that: (a) the cervix was enlarged twice the size of the uterine body; (b) the uterine cavity was also slightly enlarged; (c) normal endometrium (Figs. 1 and 2).

These ultrasonic findings, in conjunction with the history and the fact that the patient experienced dysmenorrhoea-type pains, although the menstrual periods were absent for the last ten months, established the diagnosis of haematocervix with a degree of haematometra.

Dilatation of the cervix was performed and 150 ml of chocolate coloured blood was obtained.

Four months later she was well with normal and regular periods.

COMMENT

Complications of cone biopsy of the cervix can be immediate, such as haemorrhage; or later, such as stenosis of the cervical canal, stenosis of the external cervical os, dysmenorrhoea.

Howkins (1968) suggested a slight increase in the incidence of abortion in subsequent pregnancies, but McVicar and Willocks (1968) could not confirm such a finding.

We would suggest ultrasonic examination for every case of amenorrhoea after cone biopsy of the cervix, to exclude the presence of haematocervix.

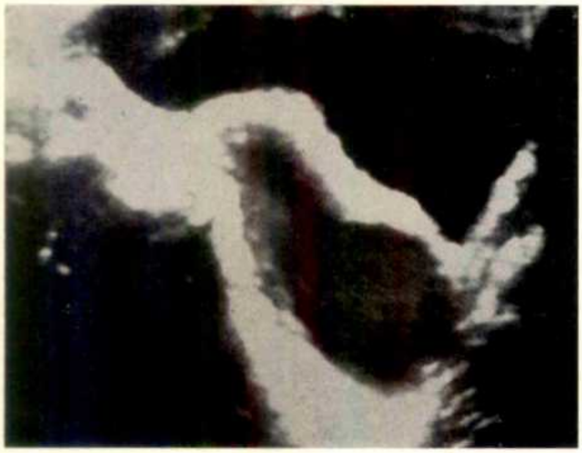

FIG. 1.

Longitudinal scan at the midline, showing the presence of haematocervix. Also note a slightly enlarged uterine cavity (haematometra).

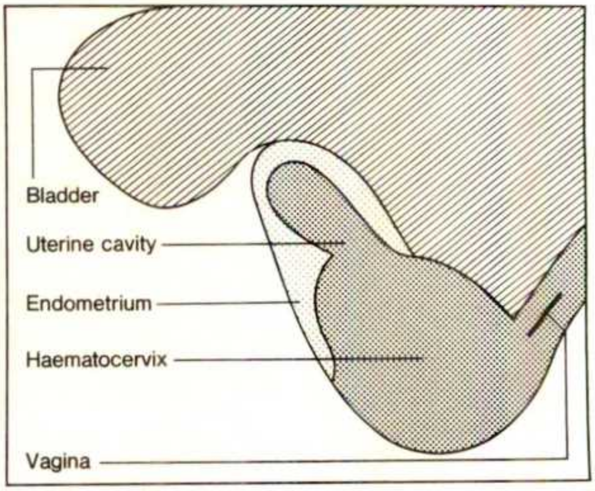

FIG. 2.

Explanatory drawing of Fig. 1.

This complication is easily dealt with by dilatation of the cervical os.

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Book review

Manual on Radiation Protection in Hospitals and General Practice. Volume 4: Radiation Protection in Dentistry. By K. Koren and A. H. Wuehrmann, pp. 52, 1977 (jointly sponsored by ILO, IAEA and WHO) (Switzerland, WHO), Sw.Fr.10

This handy volume is long overdue and fills a vacuum in the spectrum of literature available for guidance in various aspects of radiation protection. Dental uses of X-radiation constitute an area of some paradox, consisting mostly of techniques in which there is virtually no hazard, but with a small risk of considerable hazard arising from the use of outmoded techniques and faulty equipment.

In Chapter 1, p.12, a gonad dose of 200 mR is referred to as a high radiation dose, which is true only in the context of dental radiology: in fact, the maximum permissible gonad dose for the public at large is 500 mR per annum, and few patients have to undergo more than one full mouth series of films in a year, from which it is said that a dose of 200 mR can be received when little care is taken. The danger is that by occasioning unnecessary alarm to the patient one may cause more harm than good, in view of the relatively small doses involved.

The reviewer was surprised to read that the authors find it appropriate to recommend a filtration different to that recommended by the ICRP for voltages between 70 and 100 kV. The use of these excitation potentials must be so rare that it scarcely seems necessary to give a different figure, particularly as no justification is given. Synchronous motor timers are advocated, as well as electronic timers, although there are parts of the world where the mains frequency cannot be relied upon. On p.18, it is said that mechanical timers can be used provided that certain procedural modifications are observed. The history of failures associated with mechanical timers is such that their continued use cannot be advocated.

On p.21, it is most difficult to understand the purpose of a very misleading diagram entitled Peak Voltages, especially as the 100 kVp peak is shown as being 1.58 times the height of the 45 kVp peak. Lower down on the same page is the incorrect statement that exposure rate does not always bear a linear relationship to tube current, which requires qualification.

The handbook serves a useful and timely function in drawing attention to the requirements of radiation protection in what has been in many ways a neglected area, but in places it preaches a council of perfection which may be difficult to achieve. For example, in Chapter 2, p.15, reference is made to "a competent authority" to supervize matters of radiation protection which "exists in a number of countries, and can be advocated for countries where it has not yet been established". Even for countries where an organization exists, it is difficult to provide a service on the necessary scale, because of the wide distribution of X-ray units in dental practices, rather than their concentration, as in the case of departments of radiodiagnosis. One of the most valuable statements in the manual occurs in Chapter 8, p.44: "No person having a fixed workplace should be located close to the X-ray machine behind a light partition wall." This situation certainly represents one of the three most hazardous situations arising in the dental use of X-radiation, the others arising from failure of timers and the now unsual practice of holding the film in the patient's mouth.

A particularly useful section of the manual is Chapter 9, dealing with educational standards, which with reference to radiation protection, says that "it is highly desirable that operators undergo such a course even where it is not legally required".

This handbook should be required reading for dental practioners who use or are responsible for the use of X-ray equipment: however, it is certain that much of it will be difficult for the busy practitioner to absorb, and what is really needed is the availability of a back-up advisory service from the radiological protection services which exist in many large cities throughout the world. Future editions of the manual might include a list of addresses from which advice and practical help might be obtained.

D. GIFFORD

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

EXPERIENCE WITH AN AUTOMATIC ISODOSE PLOTTER

We have recently completed comprehensive beam measurements on three teletherapy machines, an SL75–10 Linear Accelerator, an F100 Mobaltron Cobalt unit and an A.E.C.L. Theratron. The S.H.M. 3-D plotting tank system* (Pitmans Ltd.) was used under the control of a PDP-8 system with extended hardware (DEC Ltd.). The controlling program was a modified version of that used at the Western General Hospital, Edinburgh for the determination of dose distributions for their planning programs (Bottrill *et al.*, 1975; Redpath *et al.*, 1976). The S.H.M. tank may also be used as a stand-alone analogue system with its own plotter; both diode detectors and ionization chambers are available. Our measurements concentrated on the use of the ionization chambers which showed significant polarity effects. As several of these systems are now available in the U.K., readers may find some comments on this and other problems helpful.

The dimensions of the tank (approximately 50 × 55 × 45 cm) are sufficient to allow large beams to be measured at standard and extended SSD. When filled with water, however, its large size and weight make it very unwieldy, and a special trolley on which it could be positioned and remain during measurement would make set-up very much easier, and avoid undue strain on treatment couches and on the tank itself. Several distortions had arisen during its year of service, probably due to handling problems; in particular, the lateral motion was not parallel to the front face. When these had been corrected, a slate base was made on which to slide the tank on and off couches and no further problems due to distortions arose.

It is a design feature of the S.H.M. drive that it can be connected to an existing incremental plotter interface which forms part of the RAD8 system. We used our local call system wiring to connect the drive unit to the interface, and chamber positioning was accurate to ~0.5 mm in all three directions, except when the carriage was near the end of its travel in the z-direction and close to the water surface, when significant backlash was noted. This meant that side-wall entry was employed for measurements on each of our machines and necessitated making an adaptor for the detector holder to reduce the minimum obtainable distance between chamber centre and front face to 1.3 cm. For measurements on the two cobalt machines, signal levels at this minimum obtainable depth were extrapolated back to the depth of maximum build-up, namely 0.5 cm.

Detector signals were carried via coaxial cables to the analogue-to-digital converters of the computer. The signal sampling frequency was approximately 1000 per sec and it was possible to vary the pulse repetition frequency of the linear accelerator between 50 and 400 pps without affecting the results. Some electrical interference was observed but at a negligible level, and there was no loss in signal levels over the lengths of cable used which were at most 60 m.

Measurements were at first confined to central axis depth-dose data. These were compared with results taken using a Farmer-Baldwin meter with a standard chamber and also a chamber of local design. Systematic discrepancies were observed which increased with decreasing local dose rate. For a 10 × 10 cm plain field on the linear accelerator with an output of 4 Gy/min the discrepancy was 1% of the maximum dose rate at the 20% depth dose level. For a heavily wedged 10 × 10 cm ^{60}Co field with an output of 0.3 Gy/min the discrepancy had risen to 2–3% of the maximum at the 20% level. These results were consistent with a constant offset in the new measurements but signal levels from the amplifiers with the beam off were very small and fine trimming did not affect the measured values. The results were not affected by altering the magnitude of the collector potential on the ionization chamber between 150 and 400 volts. Stem effects were found to be negligibly small if the cables to the detectors were arranged so that a minimum length was directly exposed to the beam.

Equal and opposite discrepancies were then observed on reversing the polarity of the collecting voltage and, by averaging normalized data for the two polarities, we obtained depth dose values within 0.5% of previous measurements, for depths less than 25 cm and within 1% for depths greater than 25 cm. Preliminary measurements with the diode detectors also suggested discrepancies of a similar magnitude, and we decided to measure all our fields at both polarities using the ionization chambers. In future, we would choose to store unnormalized data as the averaging of normalized data is not strictly correct and, in addition, the raw data would allow a much fuller analysis of system performance and output characteristics. Data collection times per field for each polarity for a central axis depth dose scan and five profiles varied from 4 to 10 min. depending on dose rate, and, consequently, long measurement sessions were needed. Time could be saved in future without losing accuracy by allowing the sample number at each point of interest to vary inversely with the local dose rate.

We found the measurement programme rewarding but time consuming, and potential users should expect to take some time for familiarization. When the system is shared, it seems wise to allow a short review period for preliminary checks on the data before release of the tank.

We would like to express our gratitude to Mr. D. J. Kidney for kindly allowing us to make use of the plotting tank system purchased by the D.H.S.S., and to Dr. Bruce Vickery for his assistance in implementing the software. We shall be happy to try to answer any queries from future users.

Yours, etc.,
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*The plotting tank, now manufactured by EMI Therapy Systems Inc., Sunnyvale, California, is available in the U.K. from EMI Medical Ltd., Windsor House, Albert Street, Slough, Bucks.

THE EDITOR—SIR,

STATEMENTS OF THE M.R.C. ISOTOPE PANEL

Two statements published by the former M.R.C. Isotope Panel in THE BRITISH JOURNAL OF RADIOLOGY (Ellis *et al.*, 1977a and b) give rise to the most serious concern. Both statements contain a number of factual errors. The wording of both is such that established fact cannot be distinguished from opinion, in some cases highly controversial opinion.

Recommendations are given which in our view cannot be supported by the available evidence, and which could, in certain circumstances, be detrimental to patients under our care.

The remit of the first working party was to study the implementation of the "ten-day rule" in radioisotope investigations. They do not appear to have considered at all whether or not a "ten-day rule" is desirable in radioisotope investigations. The available evidence is open to more than one interpretation, and a widely held view is that irradiation of the unfertilized ovum is as dangerous as irradiation of the early embryo or fetus (Graham *et al.*, 1966; Brown *et al.*, 1976). If this view is upheld it would be illogical to adopt a "ten-day rule" unless it were accompanied by a recommendation to patients that they should not become pregnant for a period which allowed radiation damage to have an opportunity to repair. This problem is clearly amenable to direct investigation by radiobiological techniques. It would seem premature to offer advice in the absence of experimental or epidemiological evidence on the matter. It is worth noting that no case of congenital abnormality has ever been implicated from a diagnostic investigation with radioisotopes.

In any individual case it is necessary to balance the danger to the patient of proceeding with any investigation, against the benefit of acquiring the resulting information. In many situations it may be argued that if the information is required at all, it must be obtained as soon as possible. In any individual case the judgement is purely clinical. Certainly an arbitrary rule—such as the "ten-day rule"—is of no assistance in making the decision. Factors which influence the clinician are of course not only irradiation to a fetus.

An even more difficult problem is the case of patients of child-bearing age who have received long half-life radioisotopes such as Selenomethionine. It is inappropriate to apply a "ten-day rule" to the safe isotopes and not to the more dangerous ones. To say that the "ten-day rule" cannot be applied to these latter patients is merely to abrogate responsibility.

The table of typical administrations bears little resemblance to current practice. In fact a table such as this could not be of any use unless it contained many qualifications. The dose to be administered depends on the purpose for which the investigation is being performed, the size of the patient and the detecting equipment being used. Thus a dose of 50 μCi of chromium-51 would be inadequate to measure red cell sequestration in the spleen, but is adequate for the measurement of red cell volume. Similar qualifications can be made to almost every item mentioned in the list. Administration of quantities which are too small to obtain reliable diagnostic information would involve unnecessary irradiation to a patient to no useful purpose. We believe the working party have done a disservice by publishing this table.

The paper on the use of throid blocking agents is also unsatisfactory. The recommendation that 50–100 mg of potassium perchlorate should be given intravenously to patients receiving more than 5 mCi of Tc-labelled pharmaceuticals requires comment. Potassium perchlorate is one of the less soluble salts of potassium. The dangers of oral administration of certain poorly soluble potassium preparations have been emphasized (Delaney and Hoxworth, 1968; Ben-Ishay and Engelman, 1973). The intravenous administration of this quantity of potassium can induce fatal cardiac arrhythmias. Consequently the sodium salt is used. However, the need to give a thyroid blocking agent at all to patients, other than those receiving pertechnetate, is highly questionable. No doubt the recommendation for giving thyroid blocking agents arises from experience in laboratories making up their own preparations in the absence of proper quality control when high quantities of free pertechnetate may be found. The majority of laboratories today use proper pharmaceutical quality control methods and/or commercial preparations which are of high quality, and inadvertent thyroid uptake is rarely seen. It is questionable whether the very small risk of an occasional unrecognized thyroid dose justifies the routine administration of dangerous drugs such as sodium perchlorate or potassium iodide. It is certainly the view of this Society that the routine use of these agents is difficult to justify.

We regret that we are unable to accept the two reports in their present form.

Yours etc.,
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THE EDITOR—SIR,

APPLICABILITY OF THE "TEN-DAY RULE" TO RADIOPHARMACEUTICAL INVESTIGATIONS

Dr. Osborn (1977) has given us a timely reminder that the "ten-day rule" has its origin in ICRP recommendations (1966) the intention of which was that the dose to a fetus should not normally exceed 1 rem. I have myself previously pointed out (Sear, 1974) that there is, on that basis, no reason to apply the "ten-day rule" to the great majority of patients undergoing diagnostic procedures with radiopharmaceuticals. This conclusion, however, conflicts with the recommendation of the MRC Isotope Advisory Panel (THE BRITISH JOURNAL OF RADIOLOGY, 1977) that the "ten-day rule" should be applied whenever the gonad dose may exceed 50 mrad. This level is said to be chosen as corresponding to the limit of dose to the total body in the WHO/IAEA category 1 as defined in their 1973 report on the use of radioactive materials on human beings for medical research. As indicated in the abstract of that WHO/IAEA report circulated to BIR members (*BIR Bulletin*, 1975), this amount of radiation is no more than a subject might receive if, for instance, he moved from one house to another. This is not a suitable criterion for the application of the "ten-day rule". The WHO/IAEA category 2 would be more appropriate. This permits a whole body dose of up to 0.5 rem which is in the category of doses permitted by the ICRP to individual members of the public who form only a small part of the whole population, as well as being the same order as the dose permitted to a fetus.

The great majority of diagnostic procedures now utilize compounds labelled with technetium 99m for which the gonad dose is typically in the range 100 to 200 mrad. The consequence of employing a criterion at least ten times as severe as that originally recommended by the ICRP would be that the "ten-day rule" would have to be applied to the majority of patients undergoing these investigations.

No one would deny the need to apply proper precautions in the best interest of patients so as to avoid undesirable radiation exposure. However, the criteria used should represent a sensible balance between relative risks and benefits. This is especially true of the "ten-day rule" which is very awkward to apply in practice. So far no evidence has been presented which would justify the MRC Isotope Advisory Panel's recommended much severer criterion for the application of the "ten-day rule" than that originally envisaged by the ICRP.

Yours, etc.
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THE EDITOR—SIR,

INTERFACE DOSIMETRY

The study of an article in the March 1966 issue of this Journal (Dutreix and Bernard, 1966) has brought to light an error of translation that appears to have gone unnoticed.

Effectively the article summarizes in English work on interface dosimetry carried out at the Institut G. Roussy, Villejuif, France, and previously published in French in a number of articles, viz: Dutreix *et al.* (1962), Dutreix *et al.* (1964), and Dutreix and Bernard (1965).

Briefly, the authors made ionization measurements in the vicinity of a carbon/metal interface irradiated by γ rays from ^{60}Co and X rays in the energy range 10 MV to 20 MV. These measurements made possible the determination of the dose absorbed by a water equivalent medium (carbon) in contact with a body of higher atomic number. It was found that in the neighbourhood of the interface there was an extremely rapid variation of dose, characterized by the occurrence of peaks at a distance of 20–40 mg/cm^2 behind the interface. These distributions were represented graphically; the ordinate axis was labelled the ratio of ionization in material Z to the ionization in carbon in the region where electronic equilibrium is established – U/Uc in the originals. One of these plots was reprinted in Dutreix and Bernard (1966) Fig. 1, p. 206), the only difference being that the ordinate axis was now labelled the ratio of absorbed dose in material Z to absorbed dose in water in electronic equilibrium conditions—D/De. The assumption was made, therefore, that $U/Uc = D/De$. I have found reproductions of this selfsame graph in two other publications, viz: Burlin *et al.* (1973) and Spiers (1969). Both label the ordinate axis ratio of absorbed dose rather than ratio of ionization produced.

Now under equilibrium conditions the ratio of absorbed dose in copper to absorbed dose in carbon is equal to the ratio of the mass energy absorption coefficients for the particular photon energy considered. In the case of γ rays from ^{60}Co this ratio is equal to 0.92, using data obtained from Knipe (1975). This signifies that under equilibrium conditions the absorbed dose in the carbon is slightly greater than the absorbed dose in the copper. However, the graphs with relabelled ordinate axes predict this same ratio to be 1.46, *i.e.* they predict that under electronic equilibrium the absorbed dose in copper is 1.46 times the absorbed dose in carbon.

Now, one of the aims of Dutreix and Bernard's article (1966) is to investigate the underdosage and overdosage of tissue in the transition zone between tissue and a metal surface. The mistake is therefore not a trivial one.

The following shows how the discrepancy can be resolved:

$$D_Z = k\,U\,\frac{mSz}{mSair}\,\text{rad} \quad . \quad . \quad . \quad (1)$$

where D_Z = absorbed dose in a volume element of material Z

U = ionization produced in the air ionization chamber

k = conversion factor for absorbed dose in air, rad/R = 0.869

$\frac{mSz}{mSair}$ = mass stopping power ratio of material Z relative to air.

Dutreix *et al.* (1962) found that for γ rays from ^{60}Co and for the situation studied, the mean energy of the electrons which form the electron flux in the equilibrium state is of the order of 10 keV. Thus the ratio of the mass stopping powers should be calculated for a mean electron energy of 10 keV. ICRU Handbook 78 (1959) gives (table 8.6) stopping power ratios for ^{60}Co γ rays as 1.02 and 0.68–0.75 for C/air, Cu/air respectively. Dutreix and Bernard found experimentally that the ratio of ionization in carbon to that in copper under equilibrium conditions is 0.69. Using equation (1) and the stopping power ratios quoted, the ratio of absorbed dose in the carbon to that in the copper under equilibrium conditions is 0.97. This agrees well with the predicted value of 0.92 found from the ratio of the mass energy absorption coefficients.

It is to be hoped that future reproductions of the results of Dutreix *et al.*, will not contain this error.

Yours, etc.,
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THE EDITOR—SIR,

NOMENCLATURE IN SCANNING INVESTIGATION

Since radioisotope (or radionuclide!) investigations are no longer unique in having a "scanning" procedure, the term has now become ambiguous. In-patients who have left the ward "to go for a scan" are becoming increasingly difficult to trace. In Aberdeen there are separate locations for gamma camera studies, rectilinear scanning, *in vivo* uptake tests and whole body counting, ultrasonic and thermographic studies, and X-ray cerebral scanning (EMI scanner). While the efficiency of having one word for one investigation is admirable, we really ought to be qualifying the word "scan" as a routine or else abandoning it altogether. Since there is little hope of abandoning it, the simplest solution is for the people who perform the investigations to be more specific in their terminology and make the effort of saying radioisotope scan, X-ray scan, ultrasound scan or thermal scan. Within each category again simple but specific terminology would keep everyone informed for example, with radioisotope scans there are conventional views and tomographic or section views. The important thing is to establish a working terminology which everyone in the hospital will understand and *use* in the interest of the patient.

There has been correspondence in these columns recently about this topic (Farmer, 1976; Nicholson, 1976; Davies, 1977; Isherwood, 1977) but written from the rather different viewpoint of finding a name to describe and distinguish between X-ray transmission section scans, and radioisotope emission section scans. It seems to us that the problem is really much wider than this. Confusion may be caused by names based on initials (for example, TCAT and ECAT for transmission and emission computerized axial tomographs) which are only really understood by the "inner clique"; or new uses of the classical languages, which are often obscure to the uninitiated (*e.g.* zeugmatography for nuclear magnetic resonance imaging); or upon commercial names (*e.g.* EMI scan) which will not apply in a hospital with a machine of another manufacturer. It would be better to concentrate on combinations of commonly used and accepted names of any reasonable origin. This is more likely to be acceptable and come into common parlance, thereby clarifying the confusion.

Yours, etc.,
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OPENING ADDRESS

HIGH TECHNOLOGY—LUXURY OR NECESSITY?

By Sir Douglas Black

This is a time of scientific self-doubt, sometimes quite unwarranted. Victorian pride in the achievements of science and technology has given place to concern about future sources of energy and industrial pollution of the environment. The real impact of science on medicine came somewhat later, with the discovery of X-rays at the turn of the century, the control of diabetes and pernicious anaemia, and the elaboration of antibiotics representing notable mile-stones; but reaction has already set in, with criticism of modern medicine in general and of high 'technology' in particular.

The value of modern medicine has been questioned by exponents of social medicine, and the traditional role of the doctor in society has been subjected to analysis by sociologists. There is of course some substance in each of these criticisms, otherwise they would scarcely have been made by serious professionals. McKeown *et al.*, (1975) are right in drawing attention to the preponderant role of public health measures in improving the expectation of life in modern society, and Cochrane (1972) makes substantial criticisms of the effectiveness and efficiency of current medical practice. Similarly, sociologists find just grounds for concern in the more authoritarian aspects of medical practice and in the lack of adequate communication between a doctor and his patients, whom they describe, not altogether happily, as 'clients'. At a more popular level, Illich (1975) has mounted a radical attack on medical professionalism as a means of combating ill-health, urging people towards self-reliance and acceptance of life's catastrophes such as pain and death.

With the possible exception of Ivan Illich, none of these critics advocates the wholesale dismantling of professional medicine; the thrust of their arguments is more limited, in the direction of stressing the community rather than the hospital, and emphasising the role of the patient rather than that of the doctor. In their more extreme statements they seem to overlook the element of common interest in these relationships. It is surely no little benefit to a community to have access to good hospital practice; and there must be few doctors who do not wish their patients to get better, or if this is not possible, to feel better as a result of their intervention, though tribute must always be paid to the *vis medicatrix naturae*.

One argument which is sometimes used by critics of modern medicine seems to me particularly fallacious. They point to the incongruity of advanced medical techniques in a third-world setting. This is fair enough–but why should the needs of developing countries be taken as a model for what is desirable in societies which are already indissolubly based on advanced technology in their general life-style? This argument surely founders, if on nothing else, on the common sense of patients who naturally seek out the best medical facilities available to them. On his side too it would be a poor doctor who would set aside any available aid in what is always the difficult task of doing his best for his patient, on the theoretical ground that it is not available in the villages of the Ganges delta. Moreover, the gradual progress towards better health in the third world is itself science-based—could smallpox have been eradicated without vaccination, or malaria partially controlled without insecticides and anti-malarial drugs? The catch-phrase 'delivery of health care' surely pre-supposes that there is something worthwhile to deliver; and whence is that to be derived but from greater knowledge?

Diagnosis

The specificity and potency of modern therapeutic agents serve to reinforce the proposition that treatment must be based on accurate diagnosis. The three pillars of diagnosis are history-taking, physical examination and special investigation. Naturally, their relative importance depends on the specific clinical problem; but in the type of practice with which I am familiar no one of the three can be neglected. In the present context, I would like to concentrate on the element of special investigation.

I would suggest that so far as possible the programme of investigation should follow the preliminary delineation of the clinical problem, and not be carried out on a 'screening' basis in advance of such delineation. There may be an exception to this in the area of automated chemical pathology (Whitehead & Wootton, 1974), where multiple estimates can be carried out on a single sample of blood; but even setting aside the cost-element, there seems to me some risk of developing more answers than there are valid clinical questions. The work-load of departments of radiology and of nuclear medicine is large and increasing, which must surely reinforce the clinical argument that investigations in this area should be carefully selected, according to a plan which is clear but not to the point of rigidity, since the circumstances of the illness may themselves alter.

I would also advocate a modest parsimony in investigations, because of their cost which is of two kinds. There is the 'opportunity cost', on the simple principle that if something is done, and if facilities are not open-ended, then something else must be foregone. And there is the 'human cost' to the patient, which is never negligible, though it can be lessened by adequate explanation and by the development of 'non-invasive' methods of which computer-assisted axial tomography is a notable example, much appreciated by those who have witnessed the after-effects of cerebral angiography or air-encephalography.

I would also emphasize the responsibility of investigative departments for self-assessment. Quality control has perhaps been most fully developed in laboratories of clinical chemistry, but the principle can be more widely extended. It is also important to derive measures of the 'sensitivity' of particular tests in a given clinical situation, based on the proportion of positive tests in that situation; and of their 'specificity', based on the proportion of negative tests in other situations (Sackett and Holland, 1975). While quality control is primarily the responsibility of the investigative departments, the assessment of benefit calls for collaboration between clinical and investigative departments. Specialization, so often the target of critics of modern medicine, is in fact a valuable aid in this endeavour; physicians, surgeons, radiologists and laboratory workers can come together as a team to improve the management of patients with disease of a particular system, to the great benefit of the patients. There is, of course, the danger that the initial clinical assessment may have allocated the patient's disease to the wrong system; but this danger can be avoided if specialists retain a component of generalism, either by

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continuing to do part-time generalist work or by holding on to the lessons of the general professional training which they will all have received.

It is worth noting that analysis of the investigative process does not necessarily lead to greater complexity and cost. As a concrete example that improved technology can lead to simplification, I would instance the replacement by reagent-impregnated test-papers of the side-room tests of urine which were cumbrous, messy, and even hazardous in inexperienced hands. At a more sophisticated level, study of the sensitivity and specificity of groups of tests, in conjunction with clinical probabilities, can lead to substantial reduction in the number of tests required to achieve a diagnosis with a probability near to unity (Card, 1975). The application of these principles to patients with jaundice has been exemplified by Knill-Jones (1975), and to patients with acute abdominal symptoms by deDombal and his colleagues (1975).

Conclusion

I would take this opportunity to acknowledge, and in a limited way to exemplify, the debt which as a practising renal physician I owe to departments of radiology, and more recently of nuclear medicine. This help has been both specific, in relation to many individual patients, and general, in enriching our understanding of renal disease. One method of keeping up to date is to edit a multi-author textbook—after all, you have to read each chapter three times, with a fair degree of critical attention. In this way I have learned from John Hodson the diagnostic value of renal size which can be particularly helpful in assessing the reversibility of renal failure, the importance of obstructive uropathy, and the inferences which can be drawn from the distribution of atrophy within the kidney. I am currently continuing my post-graduate course with Kelsey Fry, assimilating the advances made possible by better contrast media and improved technique, and extending it into nuclear medicine under the guidance of Keith Britton.

It is therefore on a basis of some knowledge that I return to the question in my title and venture to affirm that, on the assumption that we must do all that is possible for our patients, high technology is no luxury but a necessity which it is our duty to provide. Not uncritically of course, in view of the cost, but with discrimination. The practice of medicine is too difficult for us to be able to neglect the sources of help. Nor is it possible to stand still without in fact slipping back; if we forswear the challenges of innovation and enquiry, we condemn ourselves to a stultification of practice.

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Integrated diagnostic techniques

Chairman: Dr. K. E. Britton

Integrated diagnostic techniques, by K. E. Britton.
Ultrasound of the liver, by L. A. Berger.
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The value of hepatic angiography, by J. W. Laws.
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Ultrasonic investigation of the pancreas, by L. A. Berger.
Computed tomography in pancreatic disease, by R. A. Fawcitt, I. Isherwood, Joan Braganza and H. T. Howat.
Pancreatic arteriography, by D. Finlay and H. Herlinger.
E.R.C.P. in pancreatic disease, by A. Hadfield.
Pancreatic scanning, by H. J. Testa, Mary Prescott and Joan Braganza.

INTEGRATED DIAGNOSTIC TECHNIQUES

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A diagnostic imaging clinic depends on the physical proximity of experts and apparatus; on intelligently interrelating the results of different imaging techniques and ultimately on the development of a common waiting area, a common reporting station and common record keeping. The aim is to perform the optimal and not the maximal number of investigations in the appropriate order: non-invasive before invasive, less costly before more costly, simpler before more complicated, at the same time acknowledging the complimentary nature of imaging tests of structure and function.

The speakers were asked to discuss in what clinical problems of the liver and pancreas their technique provides useful results; in what problems their technique is unrewarding; and how their particular approach relates to the other techniques described. In reading these abstracts it should be noted that each author tends to impress the value of his chosen method and to understate its problems. Furthermore, since the speakers by effort and perserveance have become experts in their fields, it cannot be assumed that such good results will be obtained routinely. It is hoped that a multi-imaging approach to each organ and clinical problem will help to rationalize investigations and form the basis of a diagnostic imaging clinic.

ULTRASOUND OF THE LIVER

By L. A. Berger

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Ultrasound can show the portal tree in the normal, in portal hypertension and in portal vein thrombosis, the latter with an accuracy of over 95%. Normal hepatic veins can be displayed in right heart failure. The features of the Budd-Chiari syndrome were demonstrated.

Dilated bile ducts are shown with an accuracy of over 90%. Dilation of the gallbladder and common bile duct are frequently demonstrated. The cause of the obstruction is often shown. The commonest cause of failure is where a small stone obstructs the common bile duct.

Cysts of greater than 2 cm in diameter are diagnosed with 95–98% accuracy. Hydatid cysts show septa, disruption of the inner membrane and daughter cysts. A complicated hydatid cyst may resemble a solid tumour. A dead calcified cyst cannot be differentiated from other causes of calcification.

Abscesses are transonic with irregular walls. The surrounding liver is abnormal. Secondaries appear as transonic areas, areas of low level echoes, echogenic nodules and, rarely, transonic lesions with a nodule. Ultrasound may also demonstrate a variety of primary liver tumours, regenerative nodules, multi nodular hyperplasia and other lesions.

Anatomical causes of scan defects may be shown, e.g. large gallbladder, markedly dilated portal vein, and thinning of the liver anterior to the spine. Extra-hepatic masses of the kidney or adrenal can be differentiated.

In diffuse disease, ultrasound can demonstrate the extent of the disease. Ultrasound is complimentary to both isotope scanning and angiography.

COMPUTED TOMOGRAPHY OF THE LIVER

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The non-invasive technique of computed tomography (CT) has been assessed in 100 patients with liver disease confirmed by percutaneous cholangiography, laparatomy or liver biopsy. Correct diagnoses were obtained from the CT scan in 59 cases.

Differentiation between intra- or extra-hepatic origin was obtained in 21 of 23 patients with obstructive jaundice with the extra-hepatic obstructing agent demonstrated in 11 of 14 patients. Hepatic metastases or extra-hepatic primary tumours were identified in six of eight patients, but in neither case of hepatoma was the tumour identified by CT.

Of 40 patients with cirrhosis, a diagnostic scan (a small liver with or without splenomegaly) was seen in 18, while non-specific abnormalities of liver or spleen were described in a further 21 cases. 11 patients with chronic active hepatitis presented appearances similar to those seen in the cirrhotic group.

Analysis of mean hepatic density shows significant variations from the normal range where there is infiltration by iron or fat. In cirrhosis, however, the fibrotic changes are not evidenced by variation in mean density of the liver either in isolation or relative to the spleen. Spatial analysis of the original digital data shows that there is a significant difference between the mean autocorrelation function of the normal and cirrhotic liver at distances of the order of 1.0 cm. This may indicate different underlying structure in the hepatic parenchyma.

RADIOISOTOPE LIVER IMAGING

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The quality of radioisotope liver images has improved greatly since the advent of high resolution gamma cameras and technetium 99m labelled compounds. Radiopharmaceuticals are now available for both static imaging and liver function studies. However, studies by a DHSS working party, using the Williams phantom which is a series of hot and cold areas between 0.7 cm and 4.0 cm in diameter and a realistic liver phantom embedded in tissue equivalent material, have shown that although in phantom studies lesions of the order of 0.5 cm can be seen in the clinical situation the maximum lesion likely to be detected would be about 3 cm. Ultrasound examinations can certainly detect much smaller structures. Vessels of the order of a few millimetres can be seen regularly. However, small metastases are often indistinguishable from vascular structures. The differential diagnosis depends upon their position and number, so although the resolution of ultrasound is good the diagnosis of metastases often remains difficult. Often lesions which are visible on radio-isotope imaging cannot be seen on ultrasound and vice-versa, indicating the essentially complementary nature of the tests.

Attempts at using radioisotope techniques to differentiate between the various causes of cold areas on radioisotope colloid scans have not been very successful. Gallium 67 ratio subtraction scans are helpful but too expensive. Dynamic studies are relatively unsuccessful since many metastases are avascular and produce an appearance similar to cysts.

To summarize: radioisotope imaging is easy, inexpensive and fast. It is carried out completely by the technical staff. In spite of relatively poor resolution it achieves a diagnostic rate of about 80%. The combination of ultrasound and radioisotope imaging is very powerful since the former helps in differential diagnosis and can detect lesions invisible on colloid scans.

The advent of technetium-labelled radiopharmaceuticals for functional studies opens up wide horizons in the use of isotopes to demonstrate liver physiology.

THE VALUE OF HEPATIC ANGIOGRAPHY

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In addition to the dangers inherent in all forms of angiography, there are additional specific hazards in liver disease. There may be disturbances of the clotting mechanism due to prolongation of the prothrombin time or reduction in the platelets, and there is the serious potential danger of invasive procedures on all Australia-antigen positive patients. Thus non-invasive methods should be employed first and angiography only when there is a clear indication, in order to get information available in no other way.

Portal Venography. The main indications are in patients with portal hypertension especially associated with bleeding. It is essential in the assessment for surgery and is proving of value in embolisation and thrombosis of collateral channels and in the treatment of bleeding varices. Splenic venography provides good detail and the splenic pulp pressure can be measured at the same time but this procedure may be inconclusive if there is a massive shunt. It is contra-indicated when there is a bleeding tendency. For this reason, aorto-portography is being used increasingly but the detail obtained is rather less satisfactory.

Hepatic Venography. The main indication for this procedure is in the suspected Budd Chiari syndrome. Although the isotope scan may be characteristic, showing uptake only in the caudate lobe, angiography is necessary in order to demonstrate the underlying cause. This may be secondary to an underlying thrombotic tendency, to a tumour in the liver or to a web in the inferior vena cava obstructing the hepatic veins.

Hepatic Arteriography. The main indications are in the investigation of tumours and other masses in order to provide evidence of their localization, extent and blood supply. This is important in the pre-operative assessment of such patients. It is also of value in patients in whom ultrasound and isotope scans are at variance or equivocal. Hepatic angiography has undoubted value in the management of patients with liver trauma and haemobilia.

SUMMARY

So far as diagnosis is concerned, the indications for angiography in hepatic tumours are inversely proportional to the availability and accuracy of ultrasound, isotope and C.T. scans. On the other hand, hepatic angiography is essential in the pre-operative assessment of patients with hepatic tumour, trauma or haemobilia, and is proving of value therapeutically by embolization of hepatic tumours or hepatic artery aneurysm.

PORTOVENOGRAPHY IN LIVER DISEASES

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The technique, indications and complications of percutaneous splenoportovenography were described. Because of the limitations and danger associated with this procedure, the technique of Tolazoline—enhanced arterial portovenography was performed on 40 patients with liver diseases to assess the degree of opacification of the portal vein and branches. In this technique 30–40 mg of Tolazoline was injected selectively into the superior mesenteric artery, followed 45 seconds later by an injection of the contrast medium. In five patients, contrast medium was simultaneously injected selectively into the coeliac axis as well as the superior mesenteric artery. Opacification of the portal vein and intra-hepatic branches was good in 12 patients, satisfactory in 23 and poor in five.

ULTRASONIC INVESTIGATION OF THE PANCREAS

By L. A. Berger

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Grey-scale ultrasonography shows the pancreas well in 75% of patients, and sufficiently well to suggest a diagnosis in 15–20% of patients. Because of bowel gas, the rest have to be rescanned.

The normal pancreas is visualized by both longitudinal and oblique scanning and bears a close relationship to the aorta and its branches, the inferior vena cava, and the veins of the portal venous system. The AP diameter of the head of the pancreas can be 3 cm, the body and tail 2.5 cm.

In acute pancreatitis the pancreas is enlarged, ill-defined and contains low level echoes. The splenic and superior mesenteric veins are indistinct. Ultrasound is useful to monitor the development of pseudocysts and inflammatory masses. In chronic pancreatitis the pancreas is normal or enlarged. The echo pattern is abnormal, containing low level echoes and well-defined areas of high level echoes. Dilated ducts may be seen distal to obstruction of the pancreatic duct. In relapsing pancreatitis, chronic pancreatitis plus areas of acute pancreatitis are seen.

Carcinomas greater than 2–3 cm in diameter appear as ill-defined, lobulated masses. Low level echoes predominate, but high level echoes, sufficient to cause acoustic shadowing, often occur. Differentiation from chronic pancreatitis can be made, but this is often difficult. Ultrasound can reliably diagnose cystadenoma of the pancreas and stomach tumours.

Ultrasonicaly-guided percutaneous biopsy of the pancreas will improve the accuracy of diagnosis. This technique has no demonstrable morbidity. It is also used to decompress pseudocysts.

With experience, the accuracy of ultrasound is approximately 90%. In over 80% ultrasound can correctly predict the nature of the abnormality.

COMPUTED TOMOGRAPHY IN PANCREATIC DISEASE

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Computed tomography of the pancreas has been carried out on 50 patients with established pancreatic disease. A further 20 patients have been studied with particular reference to the appearance of the normal pancreas. All examinations have been carried out on the EMI whole body scanner (CT 5000) in the Department of Diagnostic Radiology, Stopford Medical School, University of Manchester.

Nine patients had a diagnosis of acute and acute-relapsing pancreatitis and were examined 1–12 weeks after the acute attack. 30 patients had a diagnosis of chronic pancreatitis and a further 11 patients had a verified neoplasm of the pancreas. The objective of this computed tomographic assessment was to identify in the abnormal pancreas changes which might be of value in prospective diagnosis.

Increase in size, irregularity in outline and patchy though heterogenous density of the pancreas imply pancreatic disease but were in no way specific to any particular disease entity. In acute pancreatitis the appearance of computed tomographic scans varied with the extent to which recovery had occurred. When resolution was complete the pancreas appeared normal, incomplete resolution being associated with non-specific swelling and heterogenous density change. The extent and precise location of pseudo-cysts in relation to adjacent viscera could be accurately delineated.

In chronic pancreatitis specific changes were duct calculi, duct dilation and large intrapancreatic cysts enabling differentiation between focal enlargement due to chronic pancreatitis and local expansion due to carcinoma.

Neoplastic infiltration regularly produced a solid mass of mixed low and normal densities. Hepatic metastases and associated pathology in the biliary system was seen in association with neoplasm and further distinguished this condition from chronic pancreatitis.

PANCREATIC ARTERIOGRAPHY

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Arteriography is a useful technique in the investigation of pancreatic carcinoma and endocrine tumours.

From reported series in the literature, the prospective accuracy of diagnosis of pancreatic carcinoma at arteriography is in the range 75–95%. In our series of 103 cases examined arteriographically to confirm or exclude carcinoma, including 36 proven cases of carcinoma, a correct prospective dignosis was made in 90%. In retrospect there was only one case, a case of obstructive jaundice, a false negative, in which a correct diagnosis could not be made.

Lesions of around 1 cm in size can be demonstrated by arteriography.

We believe that a negative and adequate pancreatic arteriogram excludes the presence of symptomatic pancreatic carcinoma except in the presence of pancreatitis or obstructive jaundice. It may be that arteriography will give the best results in relationship to patient survival if used in the investigation of patients with diabetes of adult onset, pancreatic steatorrhoea, pain and anorexia, who have had negative ultrasound investigations.

In the diagnosis of insulinomas, prospective accuracy is commonly in the range 75–95%. In the other endocrine tumours the accuracy is lower. Those lesions which are small, less than 1 cm in diameter, and those caused by diffuse hyperplasia, will not be shown by arteriography. They can be demonstrated by venography and venous sampling.

In the investigation of endocrine tumours of the pancreas we believe that arteriography and venography are essential.

E.R.C.P. IN PANCREATIC DISEASE

By A. Hadfield

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Endoscopic pancreatography remains the only way to examine the precise duct system of the pancreas pre-operatively. Its main uses are in the assessment of chronic pancreatitis and in the diagnosis of carcinoma of the pancreas. As an investigation in obscure pancreatic pain, ? pancreatitis, its use is still to be fully evaluated as the interpretation of minor changes in the pancreatogram is difficult. Several authors have commented on ageing changes in the post-mortem pancreatograms that can be confused with pancreatitis. (Kreel *et al.*, 1973; Kizu, 1977).

Pancreatography is of particular value in the assessment of proven pancreatitis, in detecting the presence and type of a surgically treatable lesion. In our experience a surgically treatable lesion is uncommon in pancreatitis. Pancreatic duct stones, strictures and cysts were detected in 7 of 33 patients with proven pancreatitis. The pancreatogram was always abnormal in chronic pancreatitis, but was normal in three of 18 patients with relapsing pancreatitis.

In pancreatic carcinoma the commonest finding was complete obstruction of the main pancreatic duct. In some cases, non-obstructive strictures could be confused with pancreatitis. Long irregular strictures favoured carcinoma and short regular strictures favoured pancreatitis, but interpretation can be extremely difficult. Pure pancreatic juice collected from the cannulated duct at the time of E.R.C.P. was examined cytologically in an attempt to help interpretation (Hatfield and Smithies, 1976).

E.R.C.P. alone was diagnostic in 28 of 38 patients with carcinoma (74%). Cytology alone was diagnostic in 21 patients (55%). Combining E.R.C.P. and cytology 36 of the 38 patients were diagnosed (95%).

E.R.C.P. remains an extremely useful investigation in pancreatic disease, but there are considerable difficulties both in the technique and in the interpretation of the findings.

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PANCREATIC SCANNING

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Radioisotope scanning of the pancreas has been used as a screening test of pancreatic function in our hospital for approximately eight years. Studies were first carried out with a rectilinear scanner and more recently with a gamma camera linked to a computer system. All patients were injected with 200 μCi of ^{75}Se–selenomethionine and with 2 mCi of ^{99}Tc^{m}–sulphur colloid to allow visual or electronic subtraction of the liver image.

Our results indicate that a normal scan excludes the presence of carcinoma and chronic pancreatitis with a probability greater than 90%, but an abnormal scan, because of a high proportion of false positive results, is not sufficient evidence of impaired pancreatic function. However, when patients with disorders associated with a high incidence of scan abnormality are excluded from consideration (diabetes, previous gastric surgery, duodenal ulcer, biliary disease), the false positive rate is greatly reduced and an abnormal scan should then be taken to indicate pancreatic disease.

Although newer non-invasive techniques such as ultrasound and computerized X-ray tomography can define pancreatic morphology, radioisotope scanning provides a further dimension by additionally assessing pancreatic function.

Proceedings of The British Institute of Radiology

Hyperbaric oxygen

Chairman: Sir Brian Windeyer

History of the working party on hyperbaric oxygen, by N. Howard.
Hyperbaric oxygen: controlled trials in head and neck cancer, by J. M. Henk.
The first cervix trial 1966–1973, by E. R. Watson.
The treatment of stage III squamous carcinoma of the cervix in air and hyperbaric oxygen, by M. B. Bennett.
Controlled trials in carcinoma of the bladder, by G. Wiernik.
Controlled trials in carcinoma of the bronchus, by J. B. McEwan and I. S. Cade.
Radiobiological considerations from the hyperbaric oxygen trials—a personal view, by J. F. Fowler.
Results of the hyperbaric oxygen trials—a personal view, by S. Dische.

HISTORY OF THE WORKING PARTY ON HYPERBARIC OXYGEN

By N. Howard

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In 1962 the steering committee for the evaluation of different methods of cancer therapy of the Medical Research Council set up a working party on clinical trials of high tension oxygen and radiotherapy. The scientific basis of the work was discussed in detail, particularly the work of Dr. L. H. Gray on hypoxic and therefore radio-resistant tumour cells. Hyperbaric oxygen was proposed as a means of raising the oxygen tension within the tumour, and so overcoming this radio-resistance. Clinically the first use of hyperbaric oxygen was by Churchill-Davidson and his colleagues, whose pioneer work is well-known to this audience.

The first meeting of the reconstituted working party was held on 10 June 1963, when I was appointment secretary, under the chairmanship of Professor Hedley-Atkins. The terms of reference were "to assist and collate various investigations into the effects of radiotherapy, using high tension oxygen; to assess results; to estimate the likely future of this type of therapy; and to act as a centre where information might be pooled". It was decided to treat tumours of the bronchus, bladder, head and neck, and cervix. The various parameters for treatment were agreed, and the protocols for treatment worked out.

The working party, under the chairmanship of Sir Brian Windeyer since 1967, consists of 12 members, but 21 others have taken part during the last 14 years. Although it has taken so long to produce a report for the Medical Research Council, the amount of work that has gone into this study should not be under-rated, and the working party has reached some conclusions, as you will hear later. 1,200 patients have been included in the trial, and when one considers that it takes about 40 minutes to treat a patient in oxygen, the work involved can readily be imagined. At the beginning of the trials the climate of opinion was such that it was difficult to have the same treatment carried out at each centre, but as the years have gone by attitudes have changed, and in the later years identical treatments have been carried out in different centres, which has of course been most helpful in reaching conclusions. Variations in such factors as fractionation have made it more difficult to be dogmatic in reaching conclusions, but has produced much interesting work in relation to other methods of radio-sensitization.

HYPERBARIC OXYGEN: CONTROLLED TRIALS IN HEAD AND NECK CANCER

By J. M. Henk

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Two trials of hyperbaric oxygen (HBO) and radiotherapy in head and neck cancer have been performed. The first trial began in 1964 using identical dose and fractionation in HBO and air, 10 fractions in 22 days, to a tumour dose of between 3,500 and 4,600 rad depending on field size (Henk *et al.*, 1970). 295 patients were admitted, all from Cardiff; there was a significantly higher local tumour control rate in the HBO series, 53% compared with 30% in the air series ($p < 0.001$), which resulted in a significantly reduced necessity for subsequent salvage surgery, but there was no improvement in survival. Normal tissues effects were also increased by HBO, especially in the case of the larynx, so no conclusive evidence of an improved therapeutic ratio could be claimed.

In the second trial, begun in 1971, the fractionation scheme in HBO was retained but the tumour dose reduced by 10% wherever the larynx was in the treatment volume. The control group received a conventional daily fractionation scheme in air. This trial has just concluded; up to June 1976 104 patients were entered from Cardiff and 23 from Leeds. Preliminary results show that both survival and local tumour control rates are significantly higher in the HBO series and there is no difference in normal tissue effects.

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THE FIRST CERVIX TRIAL 1966–73

By E. R. Watson

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This was a multicentre trial from Portsmouth, Oxford, Glasgow and Mount Vernon, on 320 histologically proven cases of cervical carcinoma. The patients were all under 76 years of age and fit for hyperbaric treatment. The majority were in Stages III and IV but a few Stage IIB cases were also treated.

The object of the trial was to compare the effects of the same dose schedule in both air and oxygen. Provided this criterion was observed the centres were free to choose their own schedules. All the cases have now completed three years follow up and over 80% can be assessed at five years.

The local recurrence rate showed a very significant improvement in favour of oxygen ($P < 0.001$). The actuarial survival rate was more modestly in favour of oxygen (all cases $P = 0.032$, Stage III only $P = 0.012$). There was no difference in the incidence of metastases ($P = 0.91$).

The incidence of adverse effects was somewhat higher in the oxygen series suggesting an overall radio-sensitizing effect on both normal and tumour tissues. Because of this it was difficult to assess the absolute effect on the therapeutic ratio. The greatest differences in survival appeared to be from the centres using a few large fractions and was partly due to poor air results with this type of fractionation.

THE TREATMENT OF STAGE III SQUAMOUS CARCINOMA OF THE CERVIX IN AIR AND HYPERBARIC OXYGEN

By M. B. Bennett

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This trial commenced on April 1, 1971. To date, 213 cases have been entered and an analysis of cases 1–185 is reported. All cases had a minimum 12 months possible survival from completion of treatment.

Four groups of patients were randomized.

Trial 3		
Group 1	In Air	5800 rad in 27 fractions × 5 weekly
Group 2	In O_2	5800 rad in 27 fractions × 5 weekly
Group 3	In Air	4500 rad × 10 fractions × 2 weekly
Group 4	In O_2	4500 rad × 10 fractions × 2 weekly
Trial 4		
Group 1	In Air	5800 rad in 27 fractions × 5 weekly
Group 2	In O_2	5800 rad in 27 fractions × 5 weekly
Group 3	In Air	4000 rad in 10 fractions × 2 weekly
Group 4	In O_2	4000 rad in 10 fractions × 2 weekly

At this stage of the trial it is possible to conclude (1) hyperbaric oxygen added to the twice-weekly fractionation scheme increases local clearance rate; (2) this does not however increase the survival rate in this group; (3) oxygen added to the daily fractionation scheme does not increase local clearance or survival; (4) oxygen does not hasten metastases; (5) there is, as yet, no real advantage of ten fractions in oxygen over 27 fractions in air; (6) the Ellis formula does not appear to work for pelvic tissues. Our original dosage scheme of 27×215 rad and 10×450 rad were both equivalent to 1775 ret. Disastrously high morbidity was found using 10×450 rad. This has been significantly reduced when the dose was reduced to 10×400 rad or 1550 ret. 1550 ret did not produce a lack of tumour control compared with 1775 ret. We believe this to be a unique trial involving studies of both the oxygen effect and fractionation in a homogenous group of patients handled by one institution.

CONTROLLED TRIALS IN CARCINOMA OF THE BLADDER

By G. Wiernik

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Two controlled clinical trials have been undertaken at Portsmouth, Mount Vernon, Glasgow, Oxford and Cape Town. In the first, from 1964 to 1971, 236 patients became available for assessment, equally divided between those treated in oxygen at three atmospheres absolute and those treated in air with a similar dose and fractionation scheme. Each participating centre was free to choose its own regime so that the maximum tissue doses varied from 3600 rad given in six fractions over 18 days, to 6000 rad given in 40 fractions over 56 days. All patients were treated by megavoltage machines and had tumours ranging from stage T1 to T4. Actuarial survival rates for the whole group have been calculated for each year of survival up to five years and no statistical differences between the two methods of treatment have emerged, there being 28% survivors at five years amongst those treated in hyperbaric oxygen and 30% survivors among those treated in air ($p = 0.72$).

The second trial has run since 1971 and has been analysed up to December, 1976, when 165 patients were assessable. For the second trial the four co-operating centres agreed on a common radiotherapeutic regime. Treatment in hyperbaric oxygen entailed a few large fractions given in a short overall time whilst the patients treated in air received many small fractions over a long overall time. Actuarial survival rates up to four years show no significant differences between the two treatment groups.

CONTROLLED TRIALS IN CARCINOMA OF THE BRONCHUS

By J. B. McEwan and I. S. Cade

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For the past twelve years randomized clinical trials have been run at Portsmouth to determine the survival rate of patients treated by megavoltage radiotherapy in high pressure oxygen (HPO) compared with those treated in air at atmospheric pressure. The trials were designed to answer the following question: "Is the survival time of certain patients with carcinoma of the lung treated with megavoltage radiotherapy in oxygen at a pressure of three atmospheres absolute as good as, better than, or worse than that of a similar group of patients treated in the same way in air at atmospheric pressure?"

With conventional small fraction daily radiotherapy, 6000 rad in 40 fractions, five fractions per week, the use of adjuvant HPO has not improved survival. When six fractions of 600 rad maximum tissue dose are given, two fractions per week, there is improved survival in HPO compared with the same dose given in air.

The survival rate in 123 patients with squamous cell carcinoma of the bronchus treated by six fractions of 600 rad maximum tissue dose in 18 days is:

Years	Air (59)	HPO (64)
2	12.4%	24.6%
4	2.5%	15.9%

Although the criteria for inclusion in the trial are designed to exclude patients with distant metastases, half the patients die in the first year and three quarters have died by the end of the second year, mostly from metastases not detected at the time of selection. Improvement in survival in the HPO series becomes evident in the second year. We now propose to continue the trial with stricter criteria for admission and will include the use of bone, brain and liver scans to eliminate patients with occult metastases in order to define a group with inoperable lung cancer whose prognosis, when treated in HPO, may be as favourable as those treated surgically.

RADIOBIOLOGICAL CONSIDERATIONS FROM THE HYPERBARIC OXYGEN TRIALS—A PERSONAL VIEW

By J. F. Fowler

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There *are* improved results to explain. The problem is to distinguish between two possible reasons for the improvement: (1) a genuinely greater enhancement of the effect on tumours than on normal tissues; and (2) equal dose enhancement ratios but a steeper response curve for tumours than for normal tissues. These possibilities cannot be resolved until data at more than one level of dose are available. The therapeutic ratio can be estimated here only by comparison with other published clinical dose-response curves:

$$\frac{\text{OER for tumours}}{\text{OER for complications}} = \frac{1.1-1.3}{1.1-1.3} \approx 1.0 \pm 0.2$$

TABLE I

HBO Trial		Net gain in local Non-Rec.	Chance probability	% Complications in HBO
Cervix (all UK patients)	320	12%	.03	12.4% (severe)
Cervix (Stage III squamous)	277	15%	.01	12.4% (severe)
Head & Neck				
(1st)	276	21%	>.001	4% (fatal)
(1st)	276	18%	>.01	9% (perichondritis)

'Net gain' is a practical way of assessing the advantage or otherwise of any new treatment. It involves counting how many patients out of 100 are lost by recurring cancer or by severe complications or both. The net gains for the HBO trials which showed an improved local non-recurrence are as shown in Table I.

These sites represent about half of the 1389 patients reported today, and about one-fifth of all the patients in HBO trials anywhere which have been reported to date. Reasons for nil results in the other trials include too small numbers, failure to randomize patients, advanced cases with too short survival, and unfavourable radiobiological design.

Those centres already using HBO should not discard it lightly. More patients benefit than experience complications. Results are still coming in. Data for lower doses in HBO are needed. These results are a considerable encouragement for other methods of dealing with hyperbaric cells in tumours, including fast neutrons and the hypoxic-cell radiosensitizing drugs. The latter should eventually provide the most definitive proof of whether hypoxic cells matter in radiotherapy, and if so for which tumours.

RESULTS OF THE HYPERBARIC OXYGEN TRIALS—A PERSONAL VIEW

By S. Dische

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There can now be no doubt that hyperbaric oxygen does increase the effect upon tumour in clinical radiotherapy. There is, however, evidence for an increased response of normal tissues. The fundamental question to be asked is: "Would the benefit have been achieved by a simple elevation of radiation dose given under normal conditions in air?" One method of assessment is to determine the percentage increase of dose in air which will produce the increment of normal tissue damage seen in hyperbaric oxygen. For tissues other than the larynx this increase is likely to be small and evidence is presented to suggest that this would be not greater than 3%. Such an increase is most unlikely to have resulted in the greater benefit in tumour control seen in the head and neck cases and in the patients with carcinoma of the cervix.

Hyperbaric oxygen appears to be beneficial in the head and neck tumours, carcinoma of the cervix and possibly carcinoma of the bronchus, but gives no benefit in carcinoma of the bladder. Almost certainly hypoxic cells are present in all the tumours treated by radiotherapy and these differences are more likely related to the differing ability of hyperbaric oxygen to sensitize hypoxic cells in the different tumours. It is to be expected that tumours at differing sites, and with differing patterns, should require differing conditions for radiotherapy as regards total dose, fractionation, overall time and means of sensitization of hypoxic cells, in order to achieve the optimum degree of tumour control. The contradictions in tumour response seen between most of the United Kingdom centres treating carcinoma of the cervix in hyperbaric oxygen with those in Capetown and Houston may be explained on the basis of different types of carcinoma occurring in different racial groups.

Where facilities for hyperbaric oxygen treatment are available, then hyperbaric oxygen would seem to be the optimum method of treatment for tumours in the head and neck region and carcinoma of the cervix. A spread of use of hyperbaric oxygen must depend upon further trials comparing this technique with newer ones which have been developed in recent years. These will include neutron therapy, the addition of cytotoxic chemotherapy and hypoxic cell sensitizers.

Hyperbaric oxygen trials have yielded a vast amount of knowledge, not only as to the place of hyperbaric oxygen in clinical radiotherapy, but also in radiobiology, the organization of clinical trials, the recording of normal tissue effects and in techniques to predict from early response the later findings so as to obtain answers in clinical trials at an early time.

Interventional radiology

Chairman: Professor G. H. duBoulay

Embolization via small vessels using a single channel balloon catheter, by C. W. Kerber.
Transcatheter embolization in liver disease, by R. Dick.
Needle biopsy of the lung, by D. J. Allison.
Needle biopsy of the spine, by P. Armstrong.

EMBOLIZATION VIA VERY SMALL VESSELS USING A SINGLE CHANNEL BALLOON CATHETER

By C. W. Kerber

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After developing meticulous techniques to prevent unwanted arterial occlusion during angiography, radiologists have begun to block arteries deliberately. These vessels supply vascular tumours and arteriovenous malformations. Basically, three methods are used. The first method is to place a balloon on the end of the catheter, guide the balloon as near as possible to the abnormality, and blow up the balloon. The balloon may be detached and the catheter withdrawn, or both may be left in place. This is akin to a surgical ligation and generally blocks large proximal feeders. It is particularly effective in the treatment of short segment arteriovenous shunts.

The second occlusive technique is the introduction of particulate emboli. Muscle, lead shot, gelfoam, silicone spheres, and other foreign materials may be introduced through the angiography catheter. One depends upon the increased blood flow of the abnormality to carry the therapeutic embolus distally. With this treatment technique, a deeper penetration of embolic material and occlusion of finer vessels is achieved. The disadvantage of this technique is that as the treatment progresses, blood flow to the abnormality is slowed, and emboli may be lost to more vascular and normal tissues with resulting ischaemic damage.

The third method is to create an intravascular cast. This experimental technique can occlude vessels at the capillary level. One infuses some polymerizing material, usually a silicone of cyanoacrylate. Control of both delivery of the agent and of its polymerization is difficult, and at this time, presents the therapist with his greatest technical problems.

We have recently developed a small balloon catheter ending in a silicone balloon. The balloon has a reinforced tip with a calibrated leak. This single lumen system allows us to inflate the balloon with the first increment of pressure and then with further pressure, to discharge fluid, either contrast agent or adhesive, distally. We have used this system to explore the intracranial arteries, and also to deposit isobutyl 2-cyanoacrylate (IBCA) into inoperable renal cancer, a traumatic renal A-V fistula, spinal cord, and intracranial arteriovenous malformations, and one carotid cavernous fistula. The patients with renal cancer were satisfactorily palliated, the renal A-V fistula and carotid cavernous fistula appear closed permanently, but the intracranial arteriovenous malformations have not been followed long enough to determine effectiveness.

The particulate occlusive techniques in use today are an effective and safe method of obliterating the blood supply of vascular abnormalities. Intravascular cast formation is still experimental, but offers us a way to obliterate the vascular tree at any desired level and awaits only further technical refinement.

TRANSCATHETER EMBOLIZATION IN LIVER DISEASE

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Newer imaging techniques of the liver, some not involving ionizing radiation, and unassociated with patient discomfort, have led to a careful re-appraisal of the place of angiography. Certainly it will always have a role in diagnosis, but indications for angiography will be very carefully appraised, and therapeutic procedures have an increasingly important role.

Arterial embolization can have a dramatic effect in life threatening situations, namely arterial bleeding or arteriovenous communications subsequent to trauma. It can staunch blood loss from an actively bleeding peptic ulcer in the patient with underlying liver disease, especially when surgery is contraindicated. Its role in liver malignancy is more controversial. A tumour should be vascular before embolization is considered. There is little point in blocking the source artery to an already necrotic tumour. Thus therapeutic embolization is probably more worthwhile in the vascular primary hepatocellular carcinoma ("hepatoma") when surgical resection is deemed impossible. Metastases are on the whole less vascular, and though a gigantic liver may shrink following embolization, and the patient's terminal weeks be more comfortable, in some cases, severe liver cell damage results and the patient's quality of life deteriorates. All patients should be carefully monitored by the clinician and radiologist in the weeks following the embolization procedure. It is unproved that the life expectancy of these patients is lengthened, but it is hoped that the rate of liver growth is halted with lessened patient discomfort.

Embolization of the bleeding gastro-oesophageal collaterals in portal hypertension is achieved following transhepatic portal vein catheterization. The complications of the procedure are low. In the initial Royal Free series of 36 procedures, the portal vein was entered in 34 (94%) and the varices sclerosed (as judged by portography at the end of the embolization) in 66%. Failure in the 33% is due to the present technical limitations of the procedure, catheter control being considerably more difficult than in the arterial system. Five of six patients followed up over three to 18 month periods did not show recanalized veins on splenic portography. Others have bled within the first few months, and have required a repeat procedure or a porto-systemic shunt. A permanent embolizing agent, probably the plastic polymer isobucrylate, should replace the present gelfoam-thrombin mixture. New collaterals opening up after the embolization are hopefully in retroperitoneal and other sites where varices are not traumatized, but regrettably new short gastric veins have formed in some patients. As with embolization procedure elsewhere in the body, selection of patients as well as of site is critical. The younger patient with one severe bleed proven to be due to varices is more suitable for collateral embolization than the terminal cirrhotic.

NEEDLE BIOPSY OF THE LUNG

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Needle aspiration biopsy of pulmonary lesions is increasingly gaining acceptance as a rapid and relatively safe diagnostic procedure (Nordenstrom, 1965). The technique may identify an opacity as being a primary lung tumour (benign or malignant), a secondary tumour deposit from a previously unsuspected or unidentified primary site, or a focus of bacterial or fungal infection. This information can clearly be crucial in determining the subsequent management of the patient.

Needle biopsy is performed with an 18 or 20 gauge needle (o.d. approx. 1 mm.), under local anaesthesia using X-ray fluoroscopic control. Bi-plane screening facilities are desirable. Rapid and careful processing of the cytological material obtained is necessary and the co-operation of a skilled pathologist is essential to the technique.

Needle biopsy is contra-indicated in the presence of emphysematous bullae, bleeding diatheses, contralateral pneumonectomy, seriously impaired lung function, pulmonary hypertension, and lesions likely to be vascular or parasitic in nature. Reported complications (Sinner, 1976; Lauby *et al.*, 1965) include pneumothorax, haemoptisis, pulmonary or pleural haemorrhage, air embolism, tumour embolism, tumour implantation, broncho-pleural fistula and empyema. Despite this alarming list of potential hazards the incidence of serious complications in practice is rare: in 70 patients examined at Hammersmith Hospital there were no deaths and only two patients required the insertion of chest drains for pneumothorax.

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NEEDLE BIOPSY OF THE SPINE

By P. Armstrong

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The technique of needle biopsy of spinal bodies and disc spaces using the Ackerman needle (Beckton Dickenson) was described. 63 patients from King's College Hospital and Lewisham Hospital underwent needle aspiration of biopsy between 1971 and 1976. A definite diagnosis was established from the material obtained in 44; in eight patients abnormal material was obtained but no definite diagnosis established.

The presentation concentrated on 22 consecutive patients with clinically suspected disc space infection, in whom disc space narrowing with adjacent bone destruction was identified on X-ray examination. A definite diagnosis of infection with isolation of the infecting organism was made in 14 patients, and in two patients malignant neoplastic tissue was identified. In the remaining six patients the procedure was unhelpful (at least three of these almost certainly had active disc space infection).

No serious complications were encountered. It was concluded that needle aspiration/biopsy of the spine is of particular value in:

(1) Cases of suspected disc space infection to establish the diagnosis and to isolate the infecting organism so that optimum treatment can be undertaken.
(2) Cases of suspected malignant neoplasm where a positive result will affect patient management.

Needle biopsy techniques cannot exclude pathological processes.

Tropical radiology

Chairman: Professor J. H. Middlemiss (University of Bristol)

A lymphographic study on chyluria, by H. Ngan.
The radiological pattern of bone infarction in the haemoglobinopathies, by J. T. Ennis.
Abdominal complications in homozygous sickle cell disease, by I. W. McCall.
Arthritis in Africa, by H. Baddeley.
Some aspects of schistosomiasis of the urinary tract, by B. C. Umerah.

A LYMPHOGRAPHIC STUDY ON CHYLURIA

By H. Ngan

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96 patients with chyluria were studied by bilateral pedal lymphography. The retroperitoneal lymphatic vessels were dilated, tortuous and increased in number in 59% of cases while the appearance of the opacified lymph nodes were abnormal in 63% of cases. Renal lymphatic reflux, either bilateral or unilateral, was seen in 93% of patients. Unilateral renal reflux was more frequent on the left than the right. A correlation was observed between the site of origin of the cisterna chyli with reference to the mid-line of the spine and the side of unilateral renal lymphatic reflux. ($P > 0.007$). There was no evidence of thoracic duct obstruction although the thoracic duct was more than 3 mm in calibre in seven cases. Lymphography was also performed on 23 patients who had had stripping of the lymphatics along the renal pedicle and upper ureter to determine if surgical disconnection was complete. Surgical disconnection was found to be complete in 95% of the 20 patients who had undergone unilateral stripping of the lymphatics, but incomplete in all three patients who had undergone simultaneous bilateral stripping of the lymphatics. The pathogenesis of chyluria was discussed in the light of the lymphographic, bacteriological and histological findings.

THE RADIOLOGICAL PATTERN OF BONE INFARCTION IN THE HAEMOGLOBINOPATHIES

By J. T. Ennis

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The haemoglobinopathies are inherited disorders of haemoglobin synthesis. In sickle cell anaemia there is alteration of the haemoglobin molecule with substitution of one amino acid for another, while in the thalassaemias there is defective synthesis of the alpha or beta chain.

The skeletal changes in sickle cell anaemia result from two factors working in opposite directions:

The hyperplastic marrow attempts to increase its volume by expansion whilst sclerosing factors attempt to replace the marrow with osteoid tissue and new bone.

The radiological pattern of bone infarction has been studied in 192 patients comprising haemoglobin SS–61 patients, haemoglobin SC–84 patients and haemoglobin S Thalassaemia–47 patients. The skeletal changes of bone infarct included articular disintegration, juxta articular sclerosis, dystrophic medullary calcification, periosteal reaction, "bone within a bone", osteolysis and in the vertebrae a central "step sign".

Age was the chief factor determining bone infarction—being seen in only 22 patients under 25 years. While high haemoglobin levels influence the severity of retinal disease in SC patients, only in the S Thalassaemia patients where there was an associated cortical thickening was there any indication of correlation. High fetal haemoglobin levels appeared to offer some protection in the SS and S Thalassaemia patients possibly by reducing viscosity. There was no correlation between the levels of irreversible sickle cells and bone infarction.

ABDOMINAL COMPLICATIONS IN HOMOZYGOUS SICKLE CELL DISEASE

By I. W. McCall

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The two main features of homozygous sickle cell disease are chronic haemolytic anaemia and vascular congestion with infarction. Both processes lead to pathological changes in abdominal organs. A prospective radiological survey was instituted to assess the incidence, radiological features and predisposing factors of these complications.

Renal changes occurred in 69% of 189 patients examined by intravenous urography. The most common abnormality was calyceal clubbing without associated parenchymal scarring. The incidence of clubbing increased with the age of the patient. Signs attributable to papillary necrosis occurred in 23% of cases. The papillary cavities were small and total papillary sloughing was not a feature.

The plain abdominal radiographs of 206 patients were reviewed and radiopaque gallstones were present in 51 (24.7%). 126 patients underwent oral cholecystography and 6 (5.3%) were shown to have radiolucent gallstones. The proportion of stones that were radiopaque was therefore 83%.

Patients with stones had significantly higher unconjugated bilirubin levels and reticulocyte counts.

Splenic infarction and congestion is common in sickle cell disease. Radiopacification was assessed on the abdominal radiographs of 188 patients and the incidence of 27.5% was found. Calcification varied between punctate, amorphous or curvilinear patterns. The size of the spleen influenced these patterns.

ARTHRITIS IN AFRICA

By H. Baddeley

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Infection assumes great importance as a cause of arthritis in tropical Africa. Suppurative arthritis due to staphylococcal, diplococcal or salmonella infection is common, brucellosis is endemic amongst cattle-rearing people such as the Masai and Karamajong and tuberculosis is rampant. Treponemal disease may affect bone adjacent to joints and gummatous necrosis of epiphyseal bone has been recognized in patients with yaws. Mycetoma due to a variety of fungal agents may invade the bones and joints of the feet and the loss of clear cortical outline of the tarsal bones that results is radiologically characteristic.

Neuropathic joint lesions due to syphilis affect the spine and large joints of the lower extremities, whereas leprosy affects the small joints of the hands and feet. Degenerative osteoarthritis is similar clinically and radiologically to that seen elsewhere in the world.

Until recently rheumatoid arthritis and gout were considered to be either extremely rare or non-existent in the native inhabitants of central Africa. However sixty patients with definite or classical rheumatoid arthritis were discovered within a one year period at Mulago Hospital in Uganda and seven patients with gout were diagnozed over a period of six years at the same hospital.

Though some of the infective causes of joint disease produce appearances that are strange to a radiologist trained in Europe, the majority of African patients with arthritis have clinical and radiological features that are quite familiar. It would be a mistake to assume that because tropical Africa is hot and sunny that rheumatic and rheumatoid disease is rare.

SOME ASPECTS OF SCHISTOSOMASIS OF THE URINARY TRACT

By B. C. Umerah

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Tissue response to Schistosomal ova is variable, ranging from florid to mild in the acute phase. Fibrosis supervenes in all progressive cases but the proportion of indigenous population with advanced diseases is relatively small due to various forms of immunity which tend to limit the course of the disease and reinfections. Hydronephrosis develops insidiously due to derangement of ureteral peristalsis but function is usually good even in grotesque cases. This is attributed to the low pressure and aseptic status; rapid deterioration of function is heralded by complicating secondary infection, or obstructing stricture, bladder cancer or calculus. Peculiarities of the ureters include gross tortuosity, continuous opacification of the ureters at urography ("montage ureterogram"), atonic ureterostasis which may be segmental in the distal thirds, bilharzial cobrahead deformity and ureterocoeles and deformities notably the "cowhorn deformity" of the lower ends of the ureters, due to mesial, cranial and anterior displacement at the vesical junctions, following trigonal and supratrigonal fibrosis. Bladder mucosal and contoural changes are more important than calcification which represents past infection. Calcification is not in the bladder wall but in dead ova; it is not a true calcinosis and the bladder remains distensible.

In Zambia where complicating strictures and bladder cancer occur, secondary infection even after instrumentation is rare; the contracted bladder has only been encountered once in over ten years and prostatic bilharziasis is mild and causes no outflow obstruction. Geographical variations of presentation is a striking feature of the disease.

Hyperthermia in the treatment of cancer

Chairman: Dr. J. F. Fowler

Introduction and some effects of hyperthermia on normal tissues, by S. B. Field.
Tumour responses to hyperthermia and the therapeutic ratio, by Fiona Stewart.
Hyperthermia and the immune response, by J. A. Dickson and S. A. Shah.
Interaction of hyperthermia and drugs, by N. M. Bleehen.
Electromagnetic heating techniques, by J. W. Hand.
The clinical effects and limitations of hyperthermia, by C. M. Ludgate, R. T. Pettigrew and W. S. Tulloch.

INTRODUCTION AND SOME EFFECTS OF HYPERTHERMIA ON NORMAL TISSUES

By S. B. Field

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The first part of this paper is devoted to a brief description of some of the effects of heat on cells and tissues and to a discussion of those aspects which indicate that hyperthermia might be useful in the treatment of cancer. The second part is concerned with the response of normal tissues to heat either alone or in combination with X rays. Three tissues are included, skin, intestine and cartilage. It is shown that heat alone causes rapid necrosis, a qualitatively different response from that of X rays. However, when lower heat "doses" are used, which are insufficient to cause direct damage, the heat may potentiate the effects of X rays but in this case the response is qualitatively similar to that of X rays alone.

For heat alone, using incidence of early necrosis as an endpoint, an increase in temperature of 1°C is equivalent to a reduction in heating time of a factor of 2, consistent with results obtained by other investigations using a variety of cells and tissues. However, the onset of necrosis with increasing temperature was very sudden, only 0.5°C being required to increase the level from 0 to 100% in the critical region. When the blood supply of the tissue is clamped, the tissue becomes more sensitive, equivalent to a factor of 3 in heating time. The significance of this finding is discussed. For heat as a potentiator of radiation damage the thermal enhancement is similar for the various tissues, increasing from unity for heating to about 40°C for 1 hour to approximately 1.8 for 43°C for 1 hour. The relationship between heating time and temperature for heat as a potentiator of radiation damage is such that 1°C is approximately equivalent to a factor of 3 in heating time (compared with the factor of 2 for necrosis caused by heat alone).

TUMOUR RESPONSES TO HYPERTHERMIA AND THE THERAPEUTIC RATIO

By Fiona Stewart

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The experimental basis for using heat in combination with X rays in the treatment of cancer was reviewed. As with any other form of therapy, no advantage will be gained unless the thermal sensitization of the tumour is greater than of the normal tissue:

$$\text{Therapeutic gain factor} = \frac{\text{Thermal enhancement ratio (tumour)}}{\text{Thermal enhancement ratio (normal)}}$$

Therapeutic gain can only be assessed if the same method and duration of heating are used for both normal tissue and tumour systems. A therapeutic advantage might be expected because of greater intrinsic sensitivity of tumour cells, or a greater sensitivity because of low pH, poor nutritional status, hypoxia or poor heat dissipation due to inefficient vasculature.

Although Overgaard & Overgaard (1974) reported thermal sensitization of tumours with no effect on the surrounding normal tissue, most workers have reported significant sensitization of normal tissues to X-irradiation (Robinson *et al.*, 1974, Thrall *et al.*, 1975, Field *et al.*, 1977, Stewart, and Denekamp, 1977). The therapeutic gain was calculated from those studies where comparable data are available for both tumours and normal tissues. No therapeutic advantage was found in three of the five studies reported when heat was applied immediately before or after irradiation (Thrall *et al.*, 1975, Stewart, unpublished and Hill 1977). A therapeutic gain was observed by Robinson *et al.*, (1974) and by Overgaard & Overgaard (1974). In two of the tumour/normal tissue studies (Stewart unpublished and Hill 1977) a therapeutic gain was achieved when heat was applied two to six hours after irradiation.

The importance of the sequence and timing of application of heat in relation to irradiation was stressed.

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HYPERTHERMIA AND THE IMMUNE RESPONSE

By J. A Dickson and S. A. Shah

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University Department of Clinical Biochemistry
Newcastle upon Tyne

Involvement of an immune response in the tumour regression that follows curative hyperthermia has been suspected since the turn of the century. There is now considerable circumstantial evidence that, in animals and in man, effective local heat treatment of a tumour can lead to regression of tumour at other sites and to cure of the host (see Dickson, 1977, for review). There are, however, indications that total body hyperthermia is less effective for the treatment of cancer, and that this may be due to a deleterious effect on the immune system (Dickson & Muckle, 1972; Yerushalmi, 1976).

In this study, 9/12 VX2 tumour bearing rabbits with metastases treated by local radiofrequency heating (LRFH, 47–50°C/30 min) at 13.56 MHz to the primary (15–20 cc), were cured. Skin response to challenge with dinitrochlorobenzene (DNCB) or KC1 tumour extract, and the anamnestic response to bovine serum albumin (BSA) and the serum titre of anti-VX2 antibody all increased following effective LRFH. These responses decreased progressively with time in untreated or unsuccessfully treated rabbits.

When curative LRFH was followed eight days later by total body heating (TBH), only 1/8 rabbits was cured. This markedly decreased survival rate was accompanied by abrogation of the stimulation of cell mediated and humoral immune responses that followed LRFH.

The data support our previous postulate that local hyperthermia leads to stimulation of an immune response against the host tumour, while total body heating depresses such a response.

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INTERACTION OF HYPERTHERMIA AND DRUGS

By N. M. Bleehen

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Oncology and Radiotherapeutics
The Medical School, Cambridge

Hyperthermia interacts with the drug treatment of tumours in a variety of ways. There may be direct potentiation of the lethal effect; a kinetic perturbation with proliferation delay and cell-age sorting, and there may be a selective effect on resting cells. There may be an increased specificity for malignant rather than normal cells. The potentiation of the lethal effect of the drug may occur at temperature/time exposures which in themselves have little effect. This potentiation may be due to altered cellular pharmacokinetics of the drug such as increased permeability of the cells, a direct synergism at the molecular targets, an effect on repair mechanism, and by direct activation of drugs or their metabolites.

Various workers have demonstrated a potentiation of the several alkylating agents *in vitro* and in some *in vivo* experimental systems. The action of bleomycin and adriamycin is also markedly increased. The mechanisms of the interactions are probably not identical. The 2-nitroimidazole/hypoxic cell radiosensitizers can also be cytotoxic for anoxic cells *in vitro* and *in vivo*. Work presented shows that this drug may show an enhanced cytotoxic effect under certain conditions of hyperthermia both for hypoxic and oxic cells *in vitro*. There is also a marked cytotoxic effect on the EMT6 tumour *in vivo*.

The relevance of these potentiating effects of hyperthermia on the action of drugs for cancer therapy in man is still uncertain, as more needs to be known about improvements in therapeutic index.

ELECTROMAGNETIC HEATING TECHNIQUES

By J. W. Hand

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Du Cane Road, London, W12

The band of frequencies in the electromagnetic spectrum which is of use in heating tissues at depth is discussed. The methods traditionally used in therapy to couple the energy into tissues are described and the disadvantages of attempting to use such methods to produce heating at depth are outlined. The possibility of producing internal hot spots in a target whose dimensions are comparable to the wavelength of the radiation and the relevance of this to the heating of small animals is discussed. Recent developments are outlined, including contact applicators which may be used at frequencies somewhat lower than the microwave diathermy frequency of 2.45 GHz, and an invasive technique which avoids the heating of superficial tissue by using needle electrodes to pass high frequency currents through deep tissue. Finally, some of the problems associated with temperature measurement in the presence of electromagnetic fields are stated and brief descriptions are given of new kinds of thermometer which enable reliable temperature measurements to be made in such an environment.

THE CLINICAL EFFECTS AND LIMITATIONS OF HYPERTHERMIA

By C. M. Ludgate, R. T. Pettigrew and W. S. Tulloch

Departments of Clinical Surgery, Anaesthetics, and Urology, Western General Hospital and University of Edinburgh

The treatment of human cancer by hyperthermia arose from the observation that spontaneous regression was often associated with intercurrent infection and prolonged high fever. Such regression may be due to a tumour necrotising substance, stimulation of the immune response, or by thermal stress.

Methods of inducing whole body hyperthermia are numerous, but the importance of a safe, easily controlled method is stressed by the deaths recorded following hyperthermic therapy to 40°C in patients for venereal disease. Using Dr. Pettigrew's method, the maximum therapeutic temperature is 41.8°C which is the critical temperature for the liver.

Heat stress was measured in standard centigrade degree minutes. This was defined as the time at one centigrade degree above the critical value required to produce the same amount of heat stress. The first fraction had to be less than 300°C minutes at 41°C standard, otherwise intravascular coagulation was induced in patients with heat sensitive tumours. Fractions at weekly intervals did not summate.

Local hyperthermia by vascular perfusion or perfusion of hollow organs was limited by the heat gradient induced, the vascularity of the tissues and whether there was neural tone in the tissues perfused. Prefusion under pressure potentiated vascular endothelial damage. Fractionation into daily treatments did not result in summation of the hyperthermic effect.

The future of hyperthermic therapy depends on knowing the survival curves for the tumours and the therapeutic ratio of potentiating factors, enabling the required combination to be calculated in terms of dosage fractions so that a safe, logical therapy could be planned.

Malignant lymphomas

Chairman: Professor A. E. Jones

Total body irradiation in the management of advanced lymphocytic lymphoma and chronic lymphocytic leukaemia, by F. M. B. Calman.
Pathology of gastrointestinal lymphomas, by K. Henry.
Gastro-intestinal lymphomas, by D. Crowther and G. Blackledge.
Radiotherapy and chemotherapy in the management of non-Hodgkin's lymphoma, by A. M. Jelliffe and Gillian Vaughan-Hudson.
Staging of the non-Hodgkin's lymphomas, by M. J. Peckham.

TOTAL BODY IRRADIATION IN THE MANAGEMENT OF ADVANCED LYMPHOCYTIC LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKAEMIA

By F. M. B. Calman

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A total of 24 patients with Stage III and Stage IV lymphocytic lymphoma have been treated with total body irradiation (TBI) at The Royal Marsden Hospital. Three different fractionation regimes have been investigated. Doses of 150–300 rad are given to the whole body in fractions of 10–15 rad over a period of 2–10 weeks (Rostom and Peckham, 1977).

The crude survival of the group of patients is 80% at four years. Fourteen patients went into complete remission lasting 3–42 months. The treatment is well tolerated by the patient and the main toxicity is haematological. The platelet count and white blood count reach a nadir approximately 50 days after commencing TBI (Rostom and Peckham, 1977). 54% of patients treated developed platelet counts below 40×10^9/litre. Of the 13 patients who developed severe thrombocytopaenia, ten had evidence of marrow infiltration by lymphoma. All patients made a spontaneous recovery of platelet count and lymphocyte count and only two patients required haematological support with platelet transfusions.

The results of TBI are favourably compared with those previously obtained in advanced lymphocytic lymphoma at this institution.

A preliminary communication reports work in progress in the management of chronic lymphocytic leukaemia with TBI.

REFERENCE

Rostom, A. Y., and Peckham, M. J., 1977. Total body irradiation in advanced non-Hodgkin's lymphoma. *European Journal of Cancer 13*, 1241–1250.

PATHOLOGY OF GASTROINTESTINAL LYMPHOMAS

By K. Henry

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As a result of a detailed morphological study of a small series of patients with primary intestinal lymphomas—including some patients with alpha-chain disease (Doe *et al.*, 1975)—in which the high incidence of plasma cell tumours was noted, a retrospective histological reappraisal of 125 cases of primary gastrointestinal lymphomas was carried out. The results of this study have shown that while the majority of these tumours are lymphocytic lymphomas, a significant proportion—39%—are essentially of a plasma cell nature. These extramedullary plasmacytomas were less common in the stomach and most common in the intestine, the majority occurring in the ileocaecal region (Henry and Farrer-Brown, 1977). Follicular lymphomas and diffuse lymphomas of both lymphocytic well-differentiated and intermediate (small follicle) cell types formed a minority group; histiocytic lymphoma proved to be a rarity and no single example of Hodgkin's Disease was encountered. Of the 125 cases, 51 lymphomas were arising in stomach, 53 in the small intestine and 21 in the large intestine including rectum. Excluding the four children in the series, ages ranged from 18 to 82 and were fairly evenly distributed across the decades.

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GASTRO-INTESTINAL LYMPHOMAS

By D. Crowther and G. Blackledge

Cancer Research Campaign, Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester

A retrospective study of the GI lymphomas seen at this hospital between 1950 and 1976 has been carried out by myself and Dr. G. Blackedge and the results are being prepared for publication. A total of 117 could be traced and of these 104 had sufficient information for evaluation.

With this information a series of possible prognostic factors were postulated. These were pathology, site of tumour, stage and treatment. The significance of these factors was assessed, using computer-plotted total survival and disease free survival curves.

The median survival for the whole population was less than two years, but 40% of those at risk were still alive and disease-free at ten years. The survival curves for favourable and unfavourable pathologies showed a highly significant difference, but the disease-free survival of the favourable group was significantly worse than the total survival, suggesting a pattern of continuous relapse which is found in this histological group in other sites.

The site of the tumour did not seem to influence survival, the median survival for tumours of the stomach, small intestine and colon and rectum all being similar. The only site where there was a significantly poorer response was in the ileo-caecal region, where no patient survived more than nine months. The spread of disease showed that each of the possible prognostic factors had considerable significance, except that local lymph node involvement did not adversely affect survival in the whole population. A possible staging classification was constructed on the basis of these findings:

Stage IA single tumour confined to gut
IB multiple tumours confined to gut
IIA tumour with local lymph node involvement
IIB tumour with local extension to adjacent tissues
IIC tumour with perforation and peritonitis
III tumour with widespread lymphadenopathy
IV tumour with disseminated disease in non-lymphoid tissue

When survival curves were plotted for each of these stages, a highly significant difference was found ($p = 0.00001$). This staging, therefore, would appear to be one which gives good separation into groups with prognostic significance.

All patients had had an initial operation to make a diagnosis, and in 50% a complete removal of tumour had been attempted, including lymph nodes. Complete surgery resulted in a much better survival, with a ten year disease free period in more than 50%. Those who had incomplete surgery did much less well. No demonstratable effect of radiotherapy post-operatively could be shown, but since this was a retrospective study the two populations were not controlled. Too few patients had received chemotherapy for this to be assessed.

RADIOTHERAPY AND CHEMOTHERAPY IN THE MANAGEMENT OF NON-HODGKIN'S LYMPHOMA

By A. M. Jelliffe and Gillian Vaughan-Hudson

The Middlesex Hospital and Mount Vernon Hospital

Comparison of treatment results between centres is hampered by histological difficulties. The British national lymphoma classification is practical and understandable and also divides cases in general into those with a good or bad prognosis (Grade I and II).

The management of non-Hodgkins lymphoma depends in part upon the stage. With localized (Stage I, II) disease, radiotherapy may be curative even with Grade II disease. In a personal series treated since 1970 after the introduction of modern methods of investigation, 11/13 Grade I and 8/14 Grade II cases remain in complete remission following localized irradiation. The value of 'prophylactic' chemotherapy in this group of patients is at present under investigation by the B.N.L.I. using Chlorambucil in Grade I disease and COP in Grade II disease.

With generalized (Stage III, IV) disease, the prognosis is very poor in Grade II cases. In a personal series treated since 1970, of 36 Grade I cases, 21 achieved complete remission and 13 remain alive and well. Of 21 Grade II cases, seven achieved complete remission and only one remains alive and well. The B.N.L.I. is at present comparing Chlorambucil with COP (Cyclophosphamide, 'Oncovin', Prednisone) in Grade I cases and CHOP (Cyclophosphamide, Hydroxyrubidomycin, 'Oncovin', Prednisone) with total body irradiation in Grade II cases. Patients with Grade I disease are achieving complete remission with equal frequency using Chlorambucil or COP and when complete remission is achieved the prognosis is similar. Chlorambucil is tolerated better than COP. With Grade II disease both methods of treatment are relatively disappointing.

Certain conclusions can be drawn. For local disease, local irradiation is essential, with very few exceptions (*e.g.* T cell childhood NHL). With generalized Grade I disease treatment is effective but lack of symptoms and slow evolution make the evaluation of treatment difficult. With generalized Grade II disease treatment is disappointing and rarely effective.

STAGING OF THE NON-HODGKIN'S LYMPHOMAS

By M. J. Peckham

Institute of Cancer Research and The Royal Marsden Hospital, London and Surrey

In Hodgkin's disease pathological staging procedures have developed as a logical extension of clinical investigative methods in the light of an understanding of the causes of treatment failure. Experience using laparotomy as a staging procedure has shown that occult splenic involvement is present in approximately one-third of patients, but involvement of the liver and marrow is uncommon.

In the non-Hodgkin's lymphomas the patient population is older and there are less well-defined clinical objectives to provide a clear rationale for intensive staging methods. However, on the assumption that accurate staging will provide a sound basis for treatment a good deal of information has already been acquired by adopting a sequential approach to staging, initially performing a marrow biopsy and percutaneous needle biopsy of the liver and proceeding, if these are negative, to laparoscopy and finally laparotomy. Employing this approach it is clear that the proportion of patients with advanced disease is considerably higher than is the case for Hodgkin's disease. Marrow and liver involvement are more common and there is a strong correlation between involvement of the marrow, liver and spleen. At the Royal Marsden Hospital, patients under the age of 60 years who have a negative bone marrow biopsy and liver biopsy are submitted to staging laparotomy and splenectomy. It is important to sample mesenteric lymph nodes since these are much more commonly involved than is the case in Hodgkin's disease. In the diffuse lymphomas the cerebro-spinal fluid is sampled for the presence of lymphoma cells.

The significance of these findings to overall patient management is being assessed and it cannot be assumed that intensive staging will lead to improved therapeutic results.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

RADIOBIOLOGY MEETINGS

The following meetings are scheduled:

"Work-in-progress", February 17, 1978;

"Recent advances in hyperthermia research", May 18, 1978.

Further information from the General Secretary, B.I.R. (01-935 6237).

SAFETY, RADIOLOGICAL EQUIPMENT AND THE LAW

A joint meeting of The British Institute of Radiology, the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology) will be held on January 20, 1978.

Further information from the General Secretary, B.I.R. (01-935 6237).

CARCINOMA OF THE BLADDER

A joint meeting of the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists, will be held on February 17, 1978 at the RSM, London, W.1.

Details from the RSM, 1 Wimpole Street, London, W.1.

COMPARISON OF DIAGNOSTIC TECHNIQUES FOR THE CHEST AND MEDIASTINUM

An evening meeting will be held on March 16, 1978 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Details and registration from the General Secretary.

BIR ANNUAL CONGRESS JOINT MEETING AND SCIENTIFIC EXHIBITION 1978

The Annual Congress will include a joint meeting with the Royal College of Radiologists, the Royal Society of Medicine (section of radiology) and the Netherlands Society of Radiology and will be held at the R.I.B.A., London, W.1. on April 13–14, 1978. Details from the General Secretary.

The "SILVANUS THOMPSON MEMORIAL LECTURE" will be delivered at this congress by Sir John Hill, Chairman UKAEA.

SECOND CONGRESS OF THE EUROPEAN SOCIETY OF NUCLEAR MEDICINE

The Institute and other UK members of the European Society of Nuclear Medicine will be hosts to this congress to be held in London April 17–18, 1978. The meeting will include a commercial exhibition, scientific demonstrations and technologists sessions. Contributions of original scientific presentations and scientific demonstrations are invited. Special abstract forms, which should be returned by December 1, 1977, may be obtained from Dr. M. N. Maisey, Nuclear Medicine Department, Guy's Hospital, London, S.E.1.

BIR CONVERSAZIONE

Will be held at Northwick Park Hospital, Middlesex on May 17, 1978.

Details from the General Secretary.

HIGH DOSE RATE AFTERLOADING GYNAECOLOGICAL IRRADIATION AS AN ADJUVANT TO GYNAECOLOGICAL SURGERY: AN ASSESSMENT OF THE CATHETRON

An evening meeting will be held on May 18, 1978 at The British Institute of Radiology (Reid-Knox Hall), 32 Welbeck Street, London W1M 7PG.

Further details from the General Secretary.

Obituary

J. G. Stewart, M.A., M.B., F.R.C.R., D.M.R.T.

Dr. J. G. Stewart, Consultant Radiotherapist at the Christie Hospital and Holt Radium Institute, Manchester, died on March 22, 1977. He was 56 years old.

He was brought up and received his early education at Peterhead, and entered Aberdeen University as a student of mathematics and physics just before the second World War. He served in the R.A.F. as a radio-communications specialist, mainly in India and, after the war, returned to Aberdeen to study medicine. He graduated in 1950 and in 1951 joined the staff of the Christie Hospital to train as a radiotherapist, being appointed consultant in 1959. He found great delight in the technical and mathematical aspects of radiotherapy and in the service he gave to his patients in the Christie, in the Manchester and Salford Skin Hospital and in Wigan Royal Infirmary. Among his many special interests in radiotherapy and radiobiology he would have regarded his studies of optimum dosage for cancer of the larynx as of prime importance and his paper on this subject, published in 1975, is already regarded as a classic.

Gordon lived his life with vigour, he had an impish and endearing sense of fun, and he could make any party swing, especially after he produced his violin. He loved a good argument, and although such discussions could be long and loud, they were never followed by bitterness or resentment. With his wife, Margaret, he entertained visitors from all over the world, and their hospitality will not soon be forgotten.

We offer our sympathy to his wife and three sons.

D. Greene.

Instructions to authors

Please keep manuscripts brief and concise and include only those illustrations essential to an understanding of the text.

Much time and correspondence will be saved if authors pay careful attention to these detailed instructions.

Material published in THE BRITISH JOURNAL OF RADIOLOGY includes full papers, case reports, technical and instrumental notes, short communications, letters to the editor and invited articles. Communications should ordinarily be addressed to the Honorary Editors, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Communications from North America or Australasia should preferably be submitted to the most appropriate of the following Associate Editors:

Dr. P. Armstrong, M.B., B.S., F.R.C.R., D.M.R.D., Department of Radiology, School of Medicine, University of Virginia, Charlottesville, Virginia 22901, U.S.A.

Dr. J. R. Cunningham,M.Sc., Ph.D., Physics Division, The Ontario Cancer Institute, 500 Sherbourne Street, Toronto 5, Canada.

Dr. H. A. Luke, F.R.C.R., F.R.A.C.R., The Alfred Hospital, Prahran, 3181, Victoria, Australia.

Dr. G. P. G. Sim, M.B., F.R.C.R., M.R.C.A., X-ray Department, Wellington Hospital, Wellington, New Zealand.

R. W. Stanford, Esq., M.A., F.Inst.P., Department of Medical Physics, Royal Perth Hospital, Perth, Western Australia.

The acceptance of a paper for publication in THE BRITISH JOURNAL OF RADIOLOGY is at the discretion of the Editors and is subject to the understanding that the material contained in the paper has not already been published and is not intended for publication elsewhere.

The Editors take no responsibility for the return of MSS, prints, etc. submitted for publication.

MANUSCRIPT. The manuscript should be typewritten in English on one side of the paper only with double spacing and margins of at least 25 mm on both sides and at the top. The top copy must be submitted together with one duplicate. The address given in the title should be that of the department(s) or hospital(s) at which the work was carried out. If any author has subsequently moved to a new address, this should be given as a footnote. Degrees and diplomas of authors should be given but not more than three for each author. Tables (numbered I, II, etc.) should be given on separate sheets, and each should have a short descriptive title. Legends for illustrations, including diagrams and graphs, should be set out on a separate sheet, and denoted Fig. 1, 2, etc. The initial letter of trade or proprietary names should be a capital. Mathematical expressions should be set out very clearly, using printed letters rather than script, especially where suffixes and indices are involved.

UNITS, SYMBOLS AND ABBREVIATIONS

Authors are encouraged to adopt the *International System of Units (SI)* (B.S.I., 1970; W.H.O., 1975) combined with the special units recommended by the International Commission on Radiation Units and Measurements (ICRU). Further details are given in *Changing to the Metric System* (H.M.S.O. 1969). The publication *Units, Symbols and Abbreviations: a Guide for Biological and Medical Editors and Authors* (Royal Society of Medicine, 1977) is thoughtful and critical on this subject; authors are strongly recommended to follow the detailed suggestions in this guide and to note particularly the comments made on the choice of units.

DIAGRAMS AND GRAPHS. Diagrams and graphs' including numerals and lettering, should be clearly drawn in indian ink on white card or blue tracing paper. The size should not exceed 355 × 304 mm. In general they will be reduced to have a horizontal dimension of 76 mm and their scale, thickness of line and lettering should allow for this reduction. Photographic prints of diagrams can also be accepted. The reproduction of graph paper requires the making of half-tone blocks and will normally not be acceptable. The figure number, author's name and title of article should be pencilled lightly on the back of each illustration.

Authors of physics papers will find advice on drawing diagrams, particularly electrical circuits, in *Notes for Authors* issued by the Institute of Physics and the Physical Society in 1976.

RADIOGRAPHS. Unmounted prints not larger than whole plate, 216 × 152 mm, and not smaller than half plate should be supplied with MSS; if the prints are not of sufficiently high standard for reproduction purposes the author will be required to submit the original radiographs and to defray the cost of making prints. Tracings of sections of prints are acceptable when necessary for additional clarification. Hospital illustrators and photographers are usually familiar with the style of drawing or print which will give the best reproduction.

COLOUR. Drawings or photographs in colour are very expensive and are acceptable only if the author is prepared to pay the additional cost of *block-making and printing*.

REFERENCES. The Harvard system is used. In the text these should consist of the names of authors and the year of publication (in parentheses). When there are more than two authors only the first followed by *et al.* should be used. In the bibliography references will be given *in full* and will include the title of the paper and the full name of the journal or other publication in which the article cited appeared. The references must be arranged in alphabetical order, in the following form:

Examples

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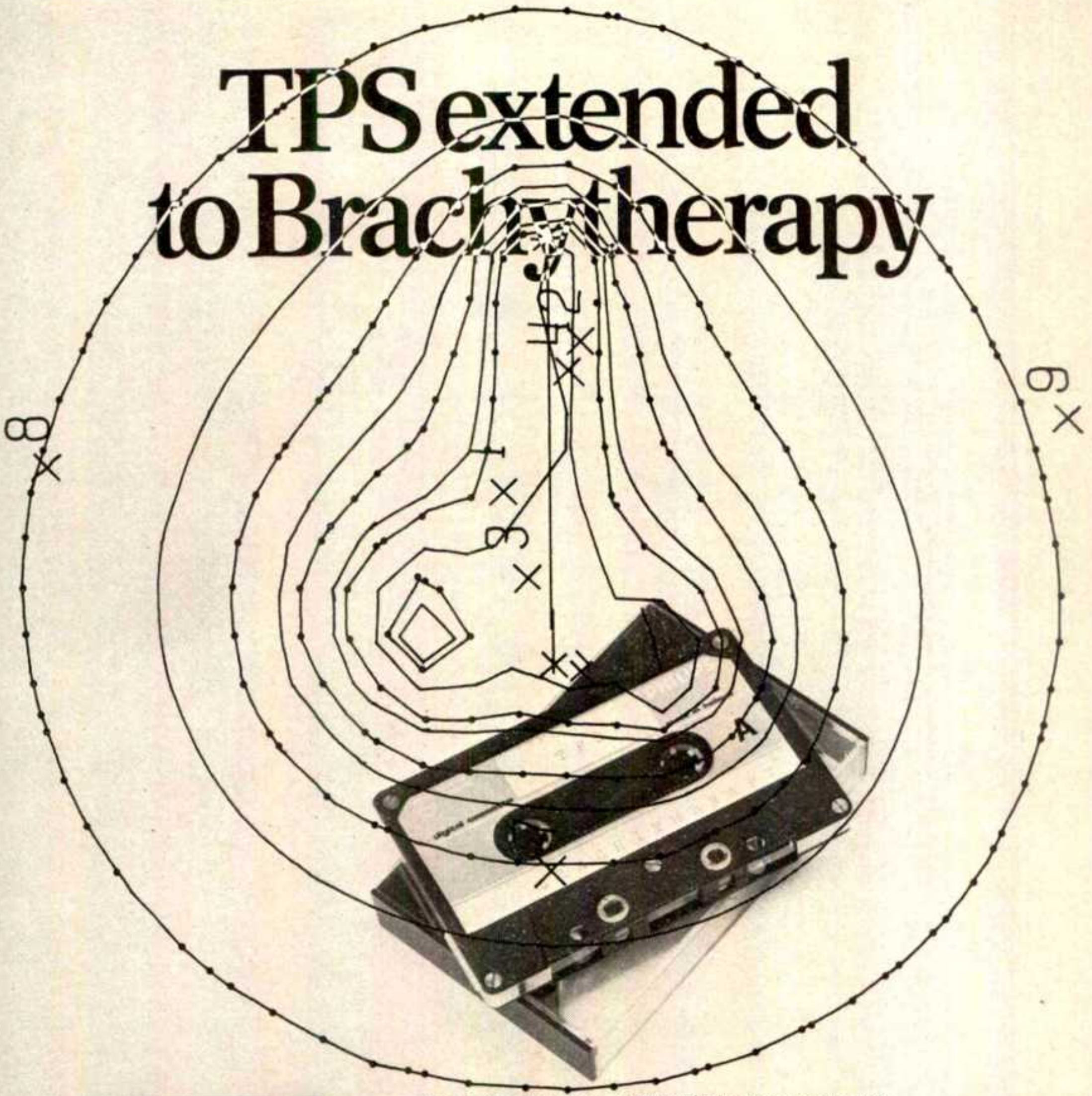

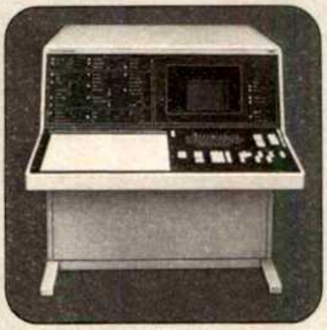

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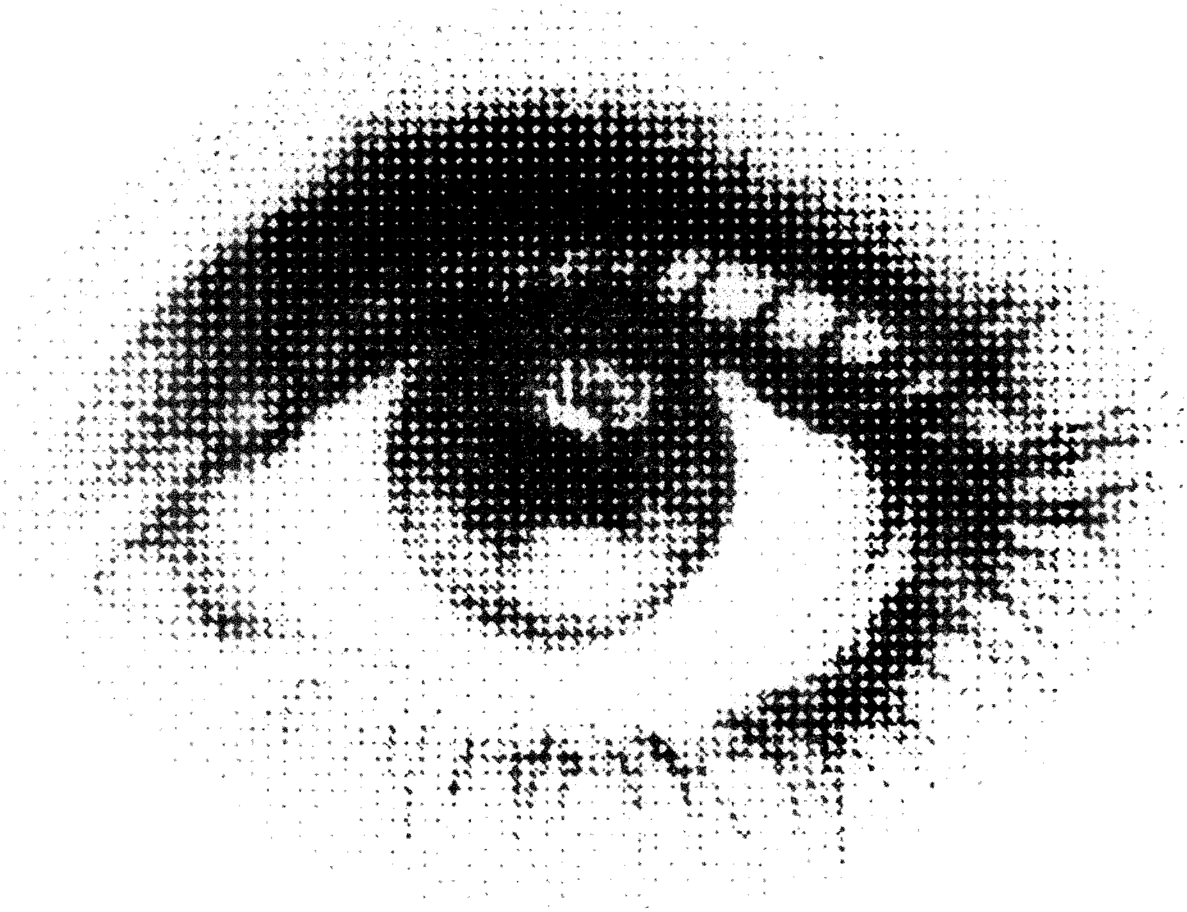

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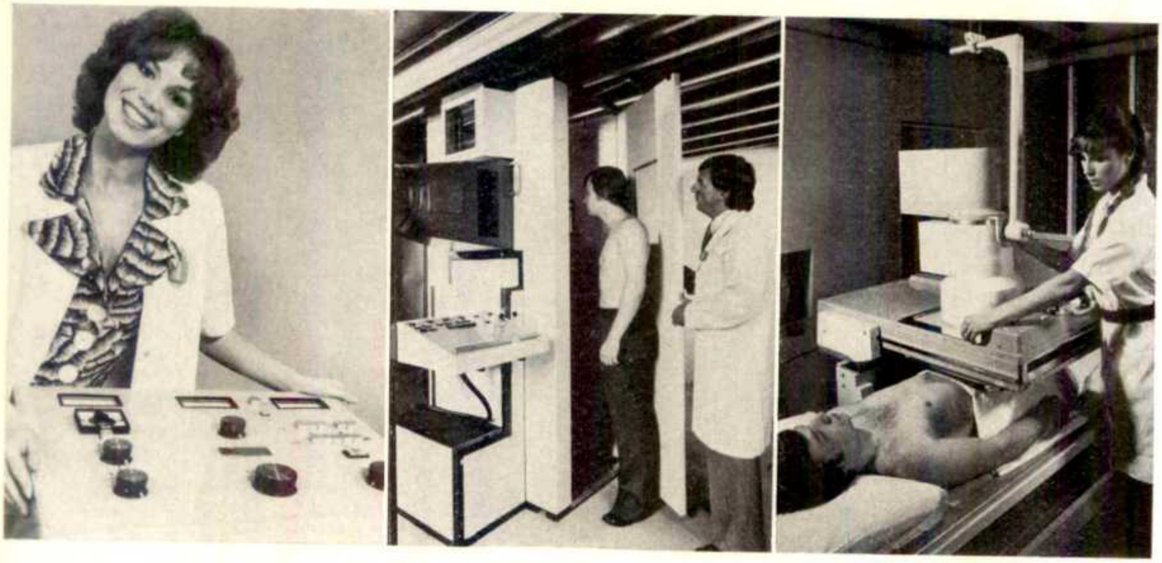

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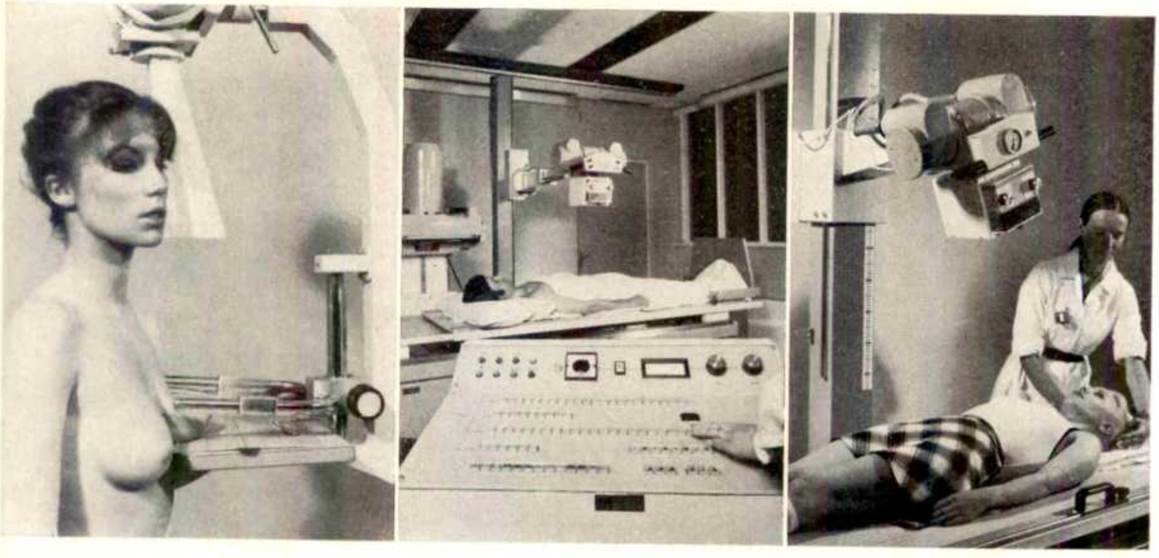

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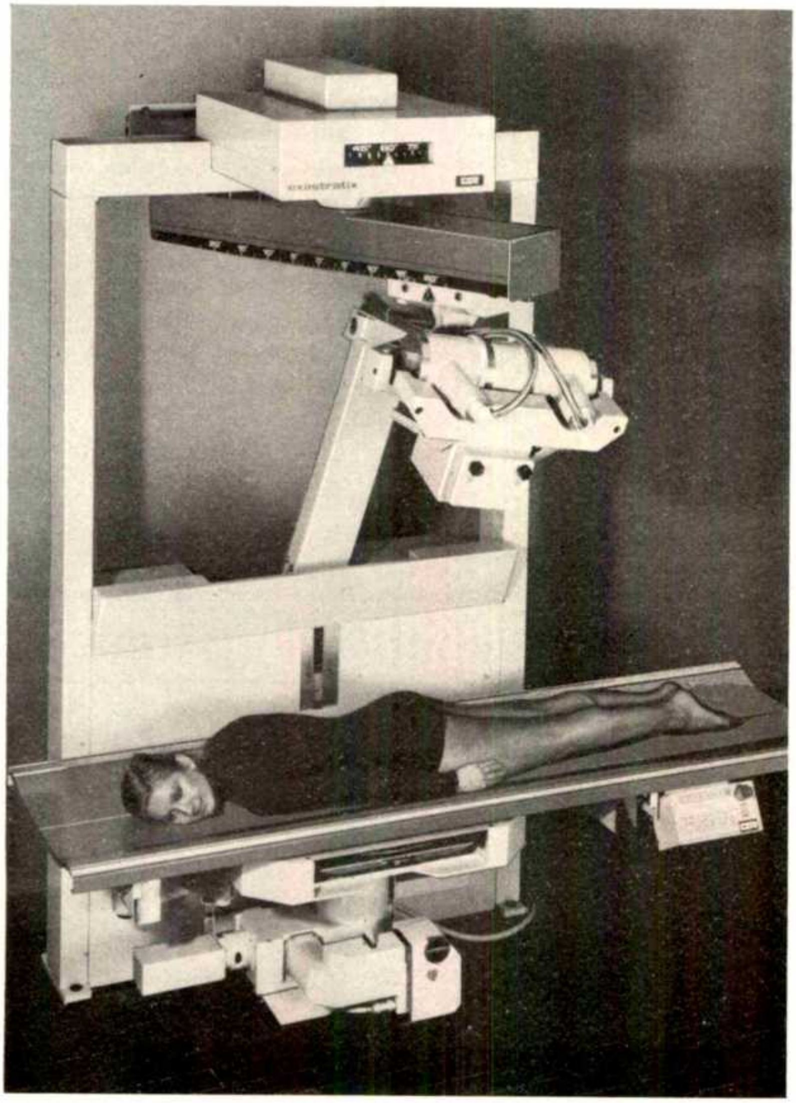

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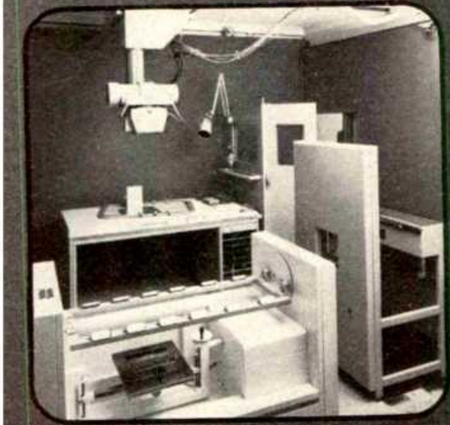

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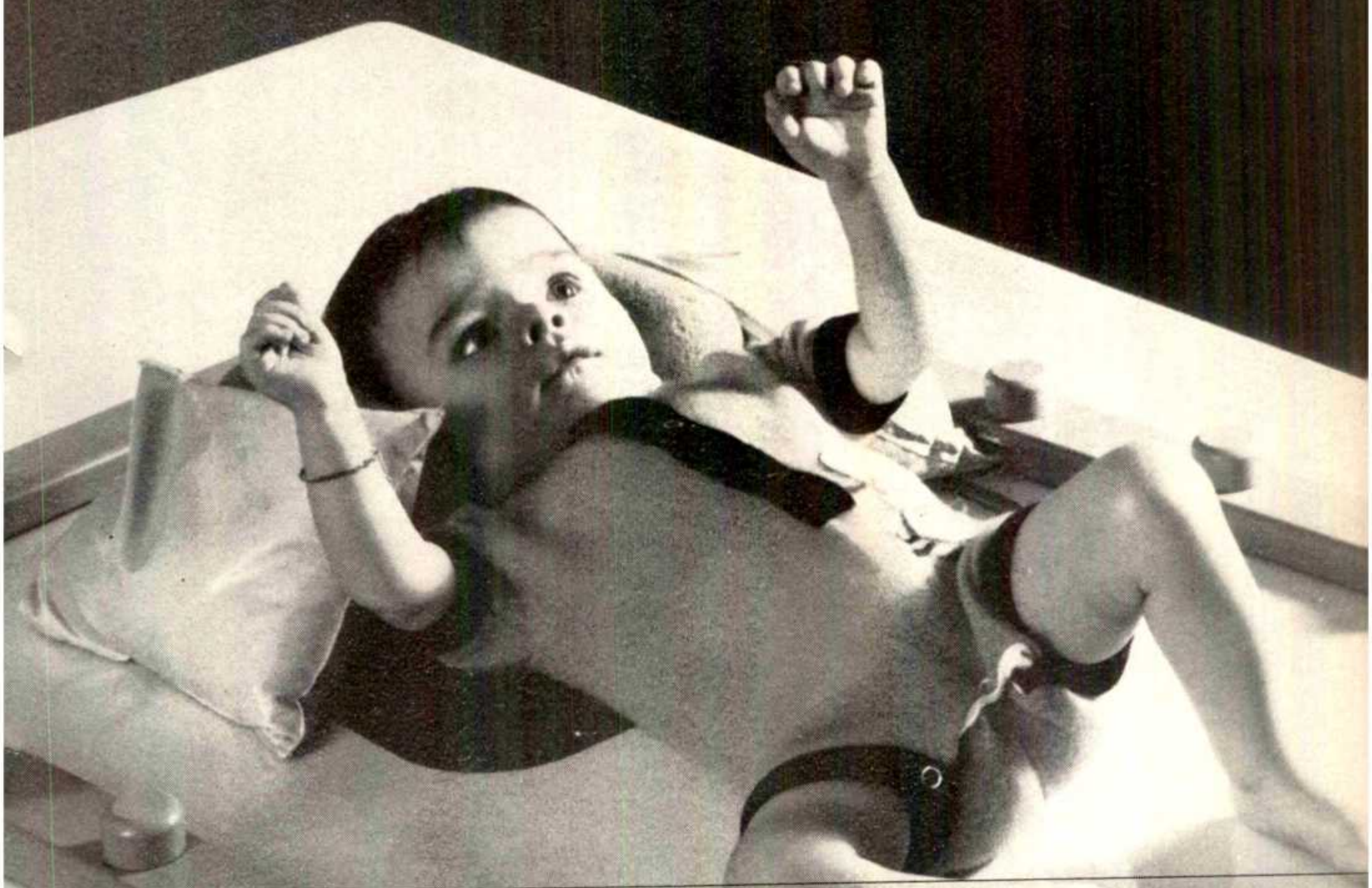

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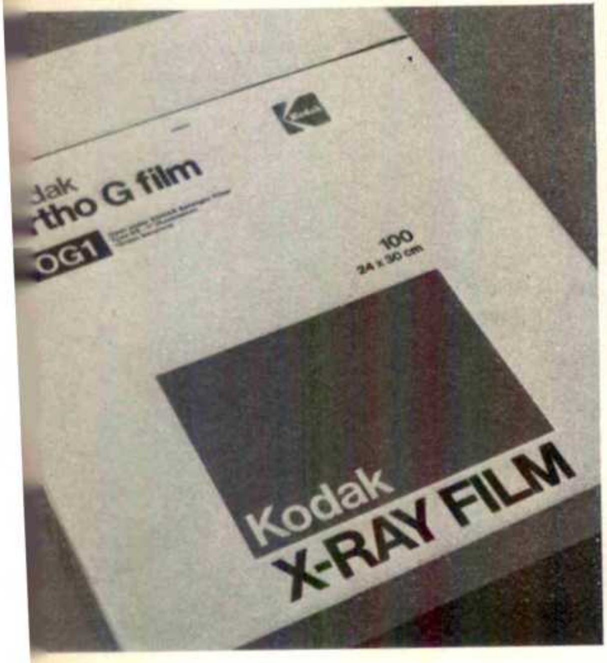

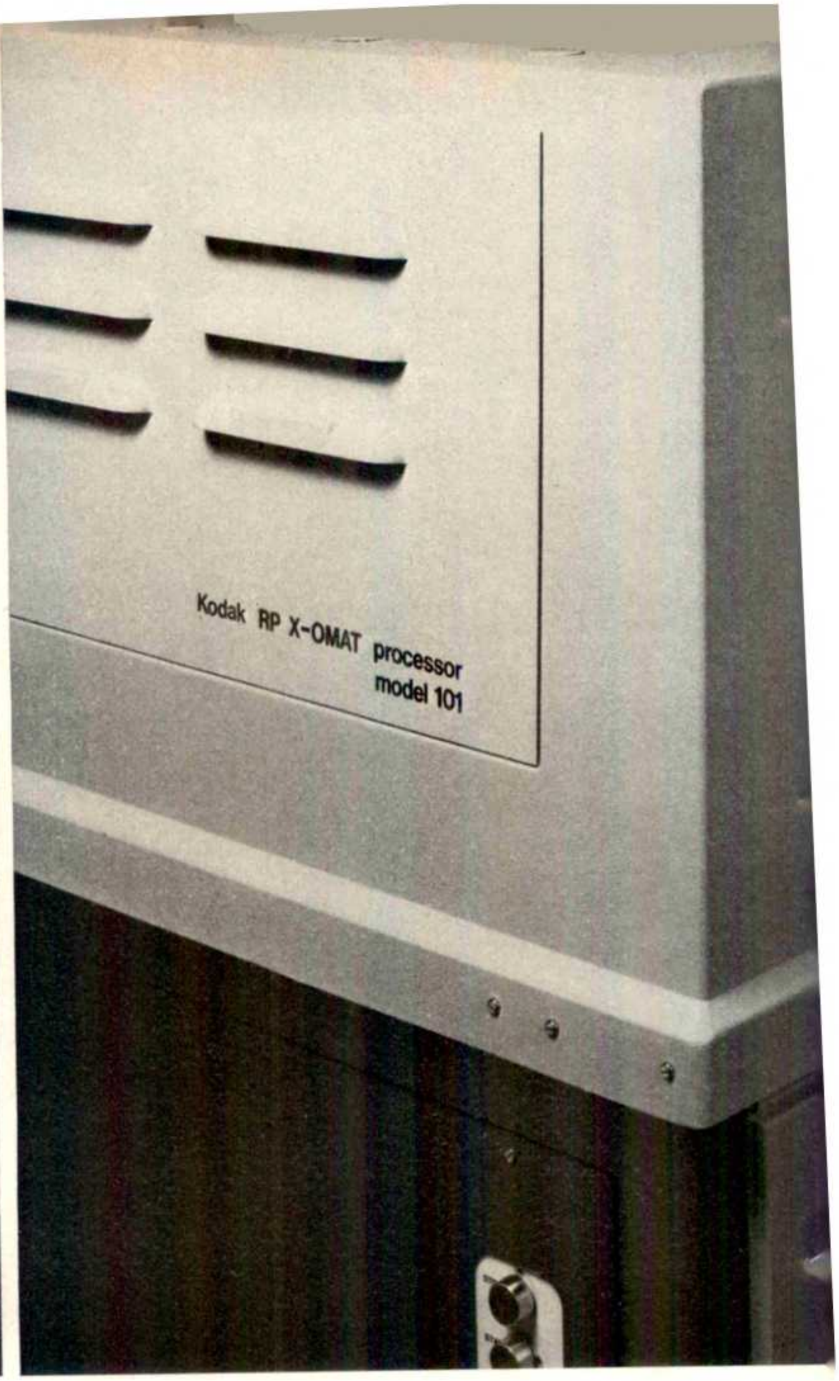

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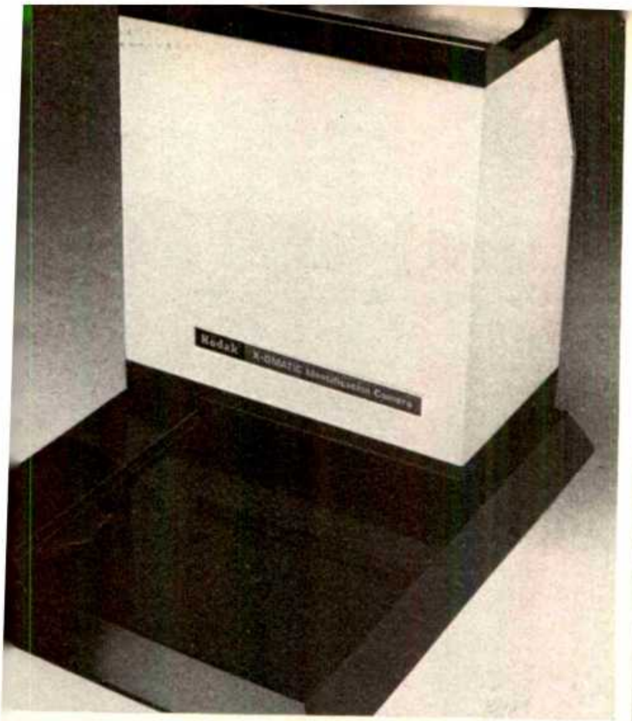

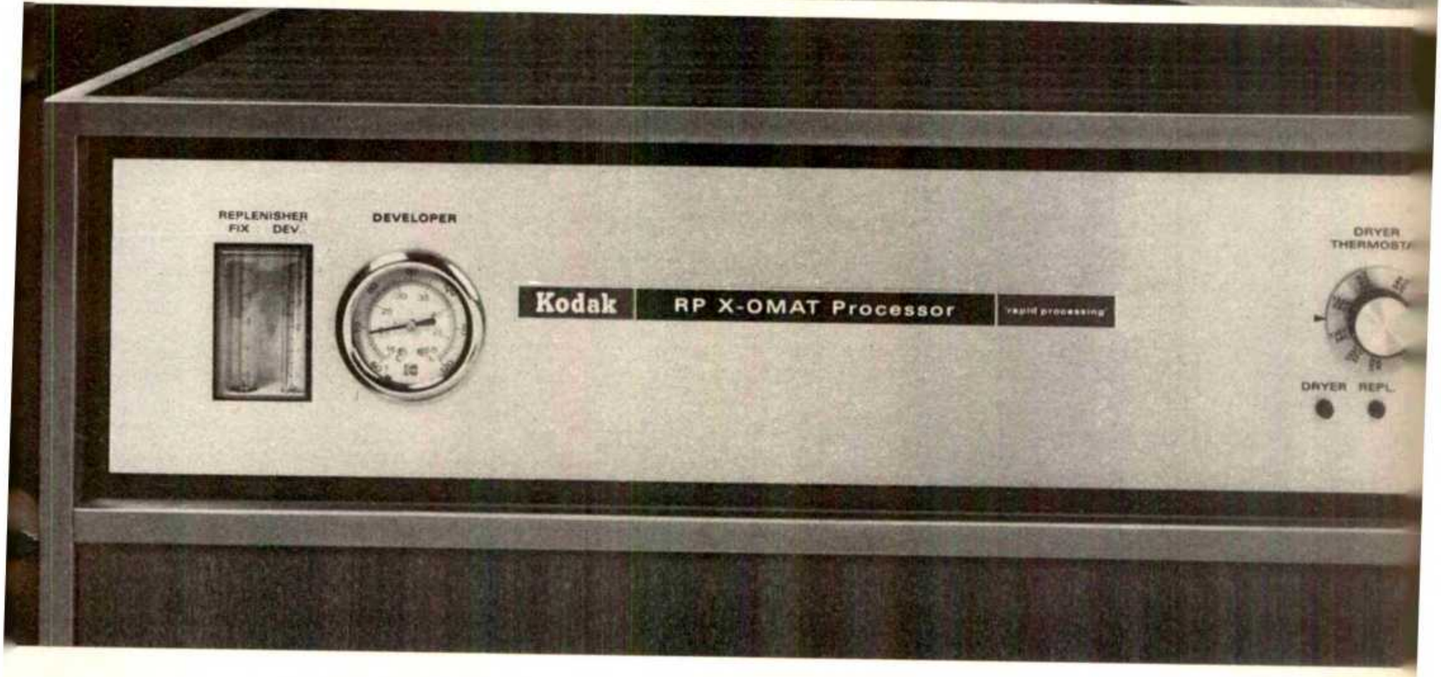

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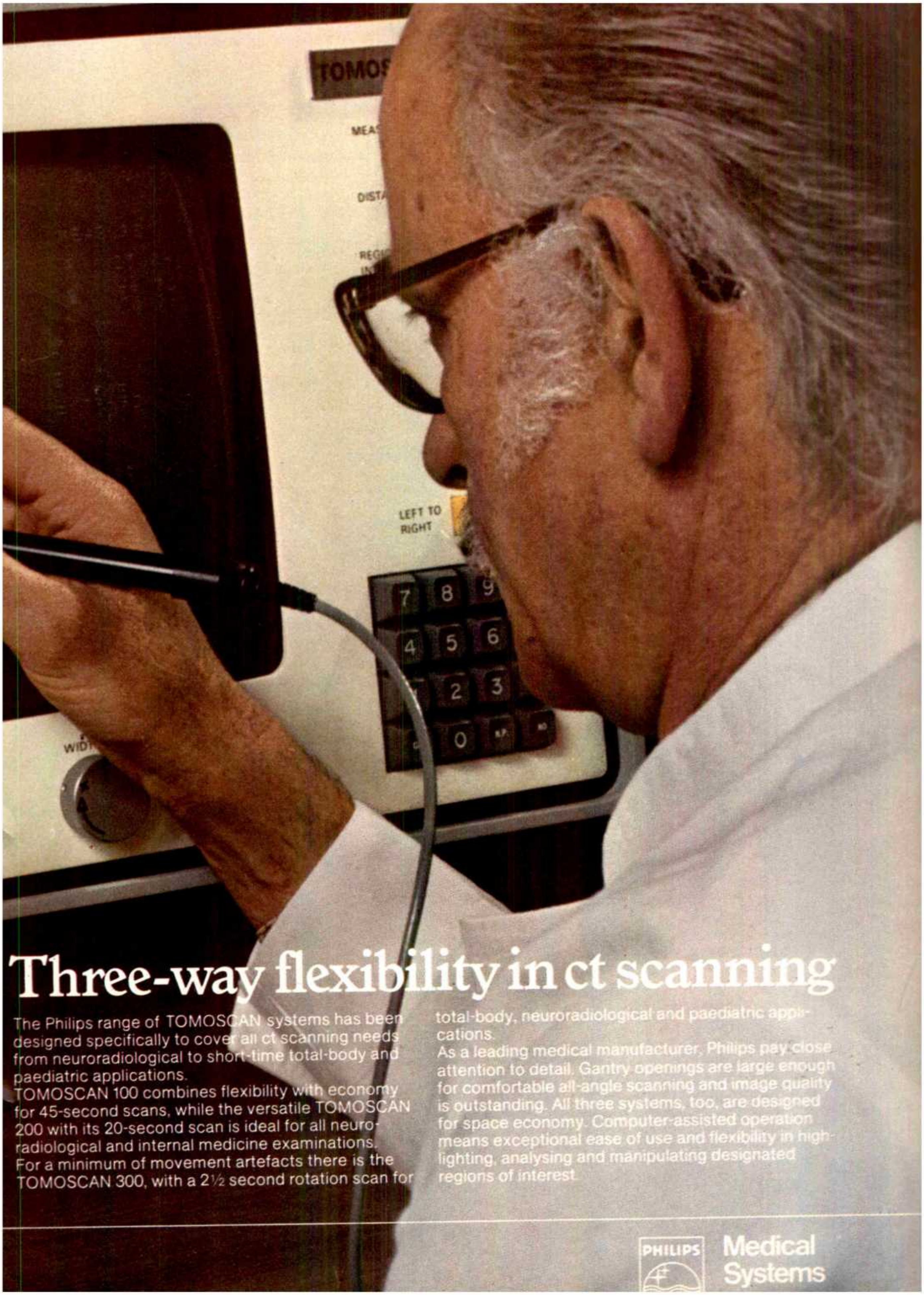

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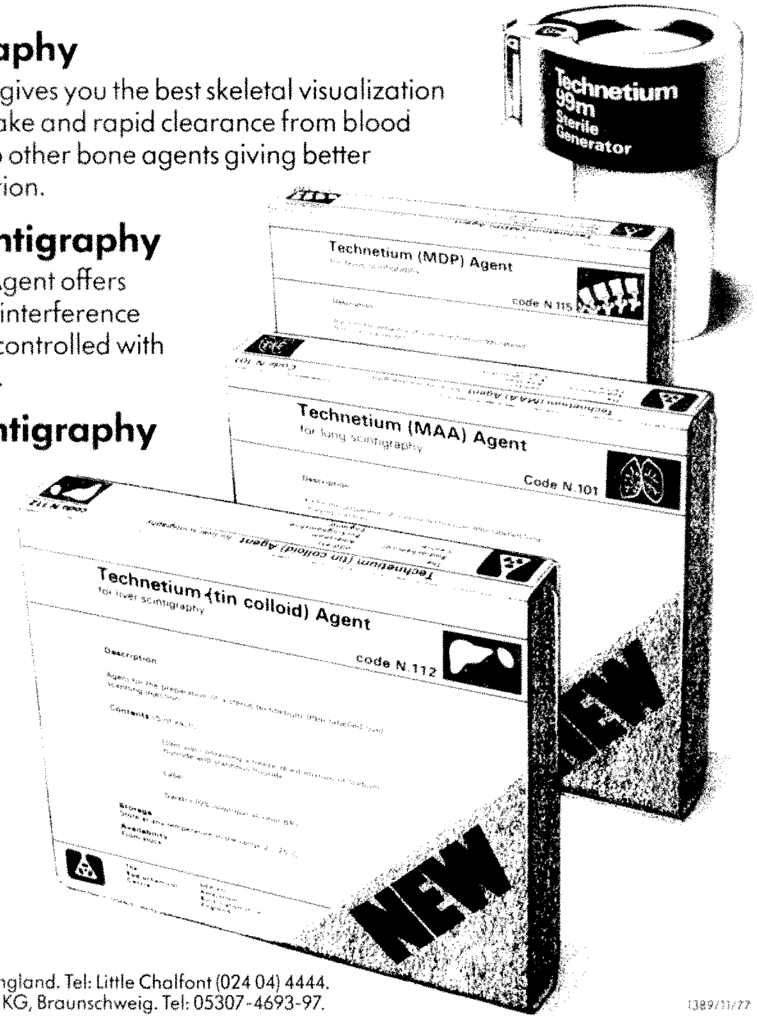

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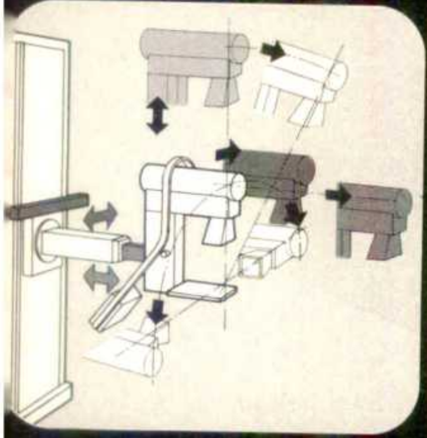

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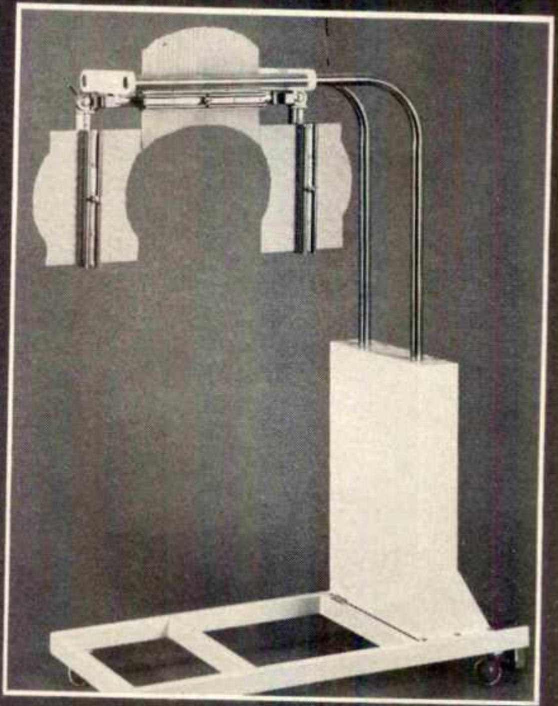

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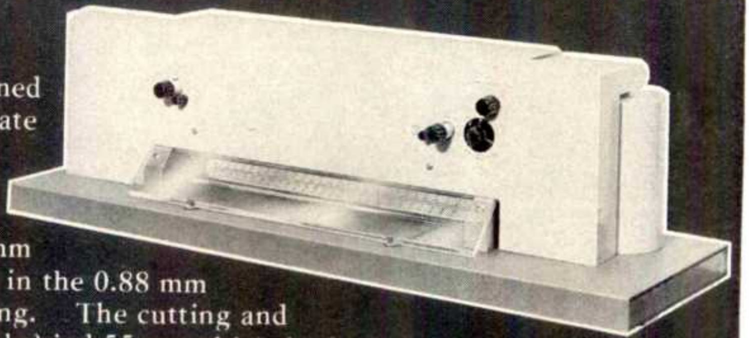

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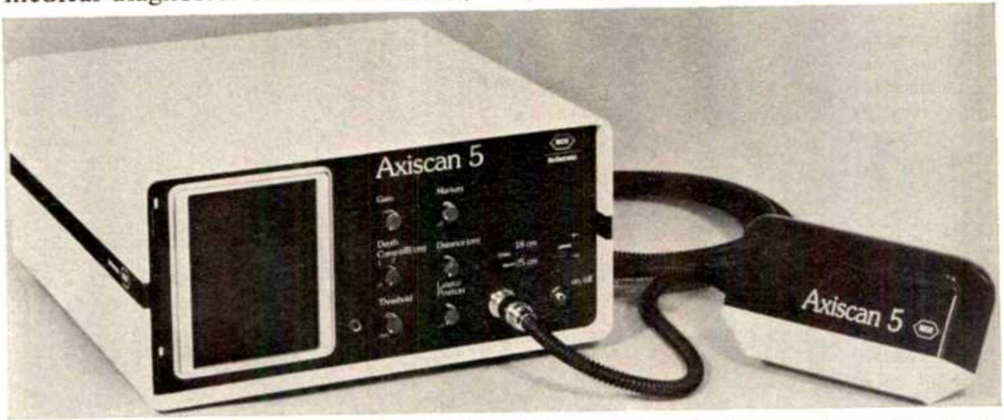

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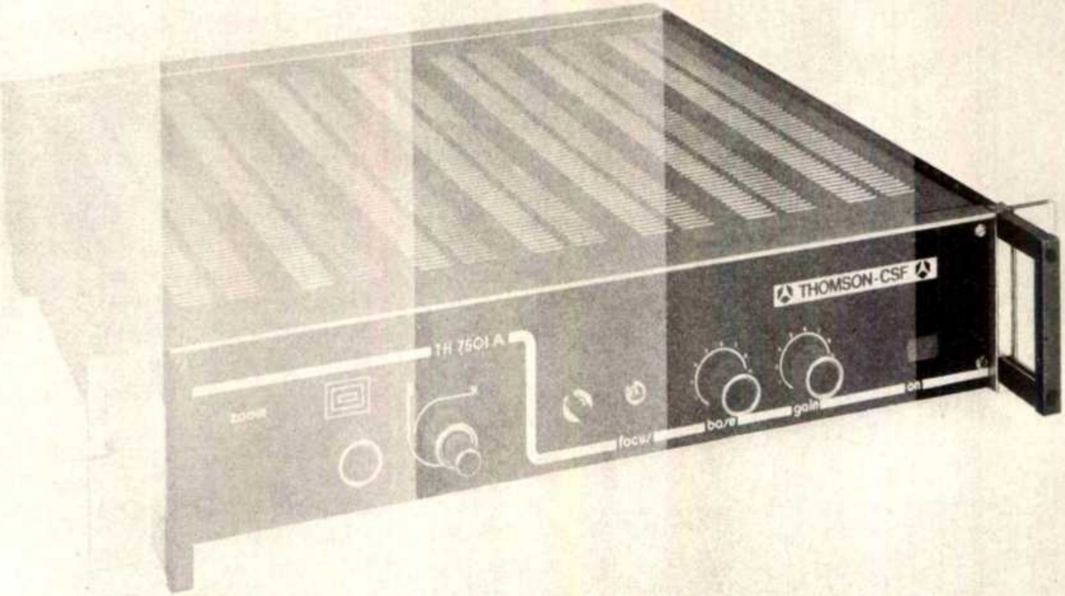

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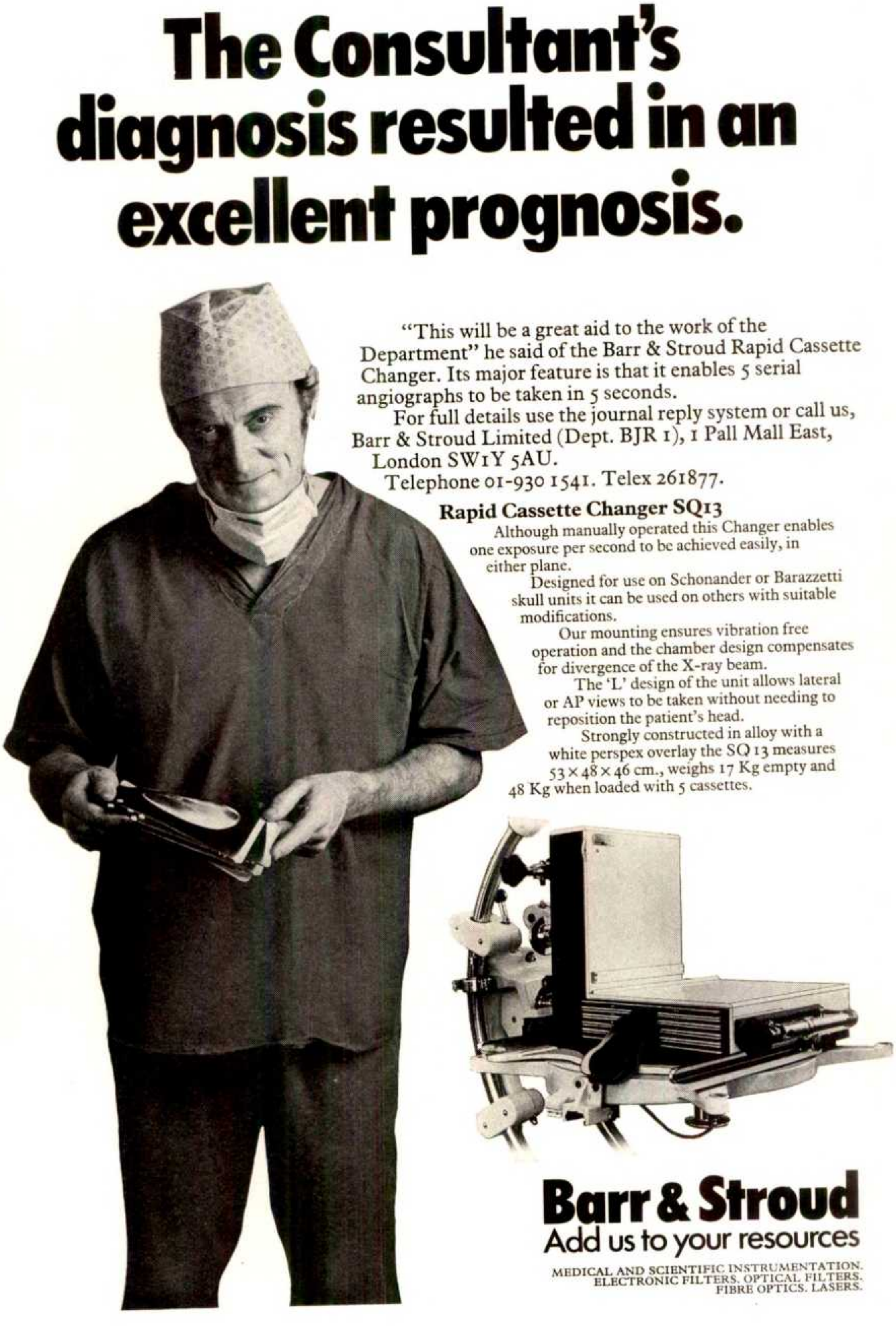

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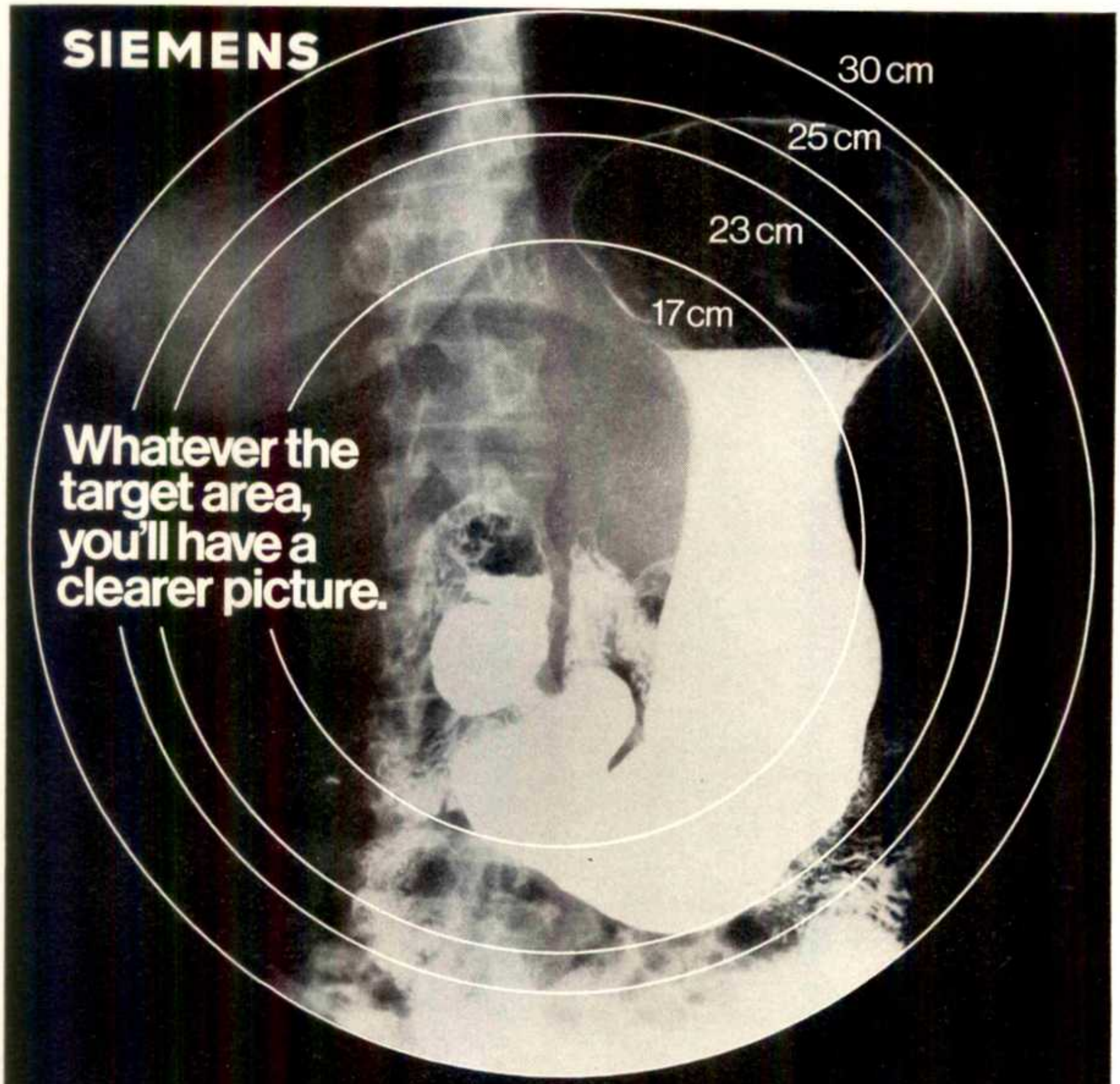

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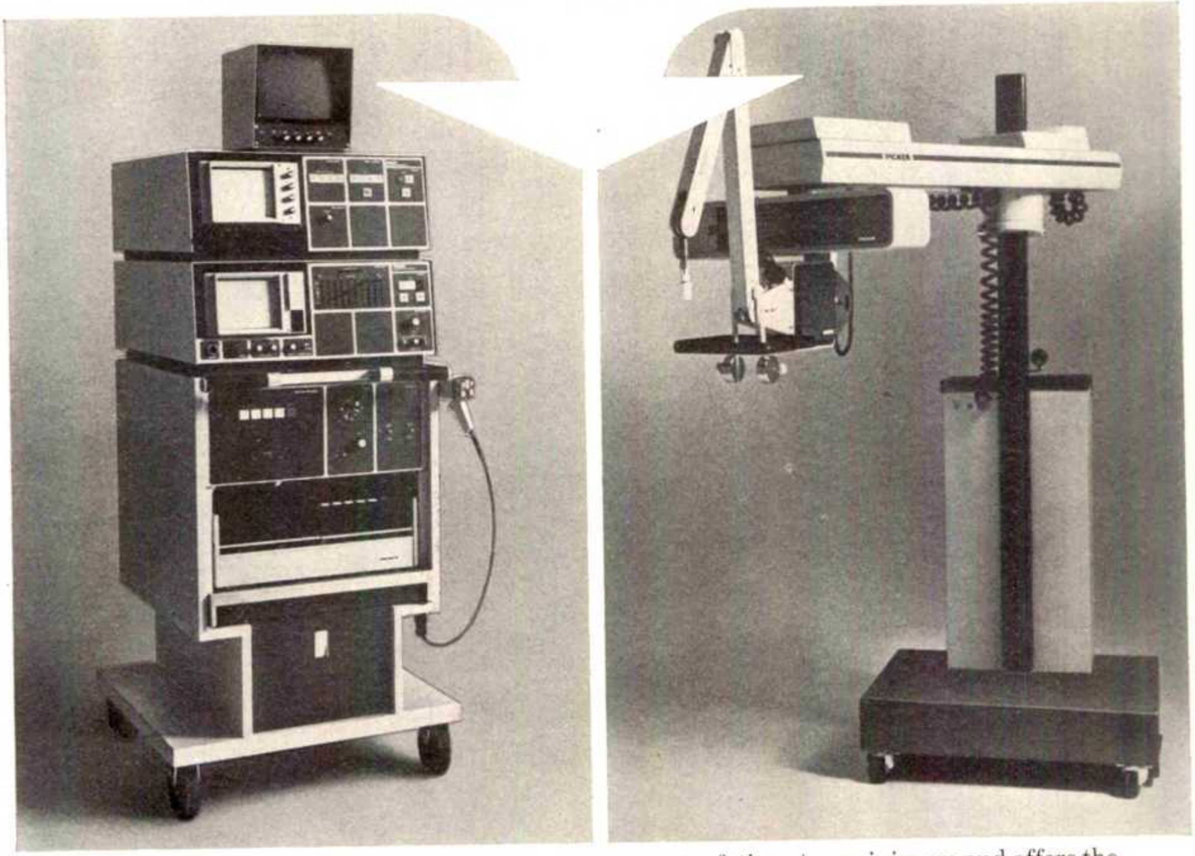

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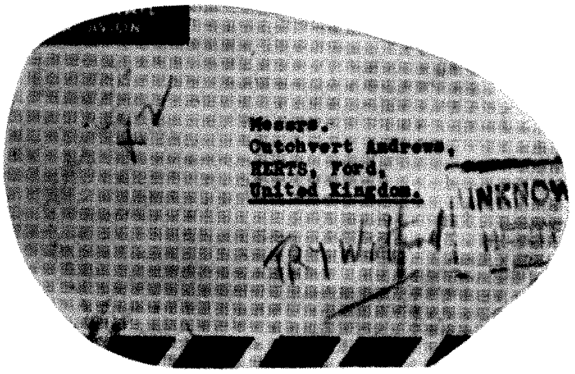

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(*Received July, 1977*)

ABSTRACT

The radiological investigation of neurosarcoidosis is discussed in relation to a series of 32 patients presenting to a neurological hospital. Cranial computed axial tomography, performed in 13 of these cases, was the most frequently positive procedure (77%). The indications for air studies are now limited but in cases with nerve or chiasmal syndromes and negative CAT they may show small mass lesions, or incomplete filling of basal cisterns due to granulomatous infiltration or fibrosis.

Sarcoid masses are avascular and angiography is only useful for exclusion of incidental tumours with pathological circulation.

Cord syndromes were present in eight cases, but myelography was only indicated in five of these and was normal in three. The cord may be involved by intra-medullary granulomas or meningeal infiltration causing arachnoiditis, both of which cause myelographic abnormalities though these are not specific for sarcoidosis.

The diagnosis of sarcoidosis is established when typical non caseating granulomas are associated with a characteristic clinical or clinico-radiological syndrome. Tissue is commonly obtained by biopsy of enlarged lymph nodes, suspicious skin or lung lesions and the liver from which positive material has been obtained in approximately 50% of cases in some series (Smellie and Hoyle, 1957). The Kveim test is positive in a high percentage (65–90%) of sarcoid cases in the active phase, but in a much smaller proportion of apparently resolved and inactive cases (Scadding, 1967) and those on treatment with corticosteroids (Mankiewicz *et al.*, 1971). Sarcoid granulomas have been found in the meninges or central nervous system in up to 14% of autopsies in cases of systemic sarcoidosis (Ricker and Clark, 1962). Most of these are silent, the incidence of clinical manifestations varying between 1–2% (Askanazy, 1952; Scadding, 1967; Silverstein *et al.*, 1965) and 8% (Mayock *et al.*, 1963), most authors finding clinical abnormalities in between 3 and 5% (Sands and Riley, 1942; Walker, 1961; Wiederholt and Siekert, 1965; Douglas and Maloney, 1973; Snyder *et al.*, 1976).

The sarcoid tissue is most commonly found in the basal meninges causing nodular granulomatous masses or adhesive meningitis, manifest clinically by cranial nerve palsies, which are usually multiple, and/or hydrocephalus due to basal cistern block or obstruction of the outlets of the fourth ventricle (Jefferson, 1957; Matthews, 1965). Less frequently the meninges elsewhere are affected, especially those of the spine, which may cause root lesions or pain. Sarcoid granulomas within the parenchyma of the brain, optic nerves and/or chiasm or spinal cord (Wood and Bream, 1959) are less common and cause similar clinical features to those of any other tumour. They are usually peripheral, suggesting direct extension from the meninges (Askanazy, 1952).

The granulomas tend to be perivascular and may extend into the adventitia and media of smaller vessels. Thrombosis has not been shown, but narrowing may be sufficient to precipitate infarctions (Reske-Nelson and Harmsen, 1962; Urich 1967; Herring and Urich, 1969; Douglas and Maloney, 1973).

Opportunistic infections may also complicate sarcoidosis (Scadding, 1967; Bosch *et al.*, 1976).

Chronic basal meningitis and/or hypothalamic syndromes occurring in cases of systemic sarcoidosis are typical enough to indicate extension of the disease to the central nervous system, if tuberculosis, which may complicate sarcoidosis (Hopkins, 1973) is excluded. Even when these syndromes are the primary manifestation, sarcoidosis is a sufficiently common cause to be considered in differential diagnosis. Other neurological lesions and raised intracranial pressure may need investigation to determine their precise cause and to decide if there is need for local therapy in cases of established sarcoidosis. If such lesions present initially they may demand investigation on their own merit.

Neuroradiological studies in sarcoidosis are mainly recorded in individual cases with positive findings or reviews of small series (De Morsier *et al.*, 1954) Bannerjeee and Hunt, 1972; Kirks and Newton, 1972; Brutec-Mikes *et al.*, 1976; Daum *et al.*, 1965; Erikson *et al.*, 1942; Robert, 1962; Semins *et al.*, 1972). We considered that it would be of interest to analyse a large series of cases presenting to a specialized neurological hospital, especially to assess the contribution of neuroradiology to diagnosis.

Material and Methods

The records of all cases of sarcoidosis which had attended The National Hospitals for Nervous Diseases were reviewed. Those with any evidence of meningeal, cranial nerve or parenchymal involvement were selected and the neuroradiological studies of these cases were analysed.

Results

Details of our 32 cases are set out in Table I.

There were 14 males and 18 females, age range 22–66 years, averaging 36 years. Twenty-six patients were caucasian, four negro and two were Guyanian indians. They were divided into two groups: A, those with an established diagnosis of previous systemic sarcoidosis at the time of meningeal or central nervous involvement—ten cases; B, those presenting intially with the neurological syndromes—22 cases.

In Group A, the interval between the primary presenting features and symptoms of meningeal involvement was two months to 12 years, average 5·2 years. In Group B, systemic sarcoid was discovered at the initial routine clinical and chest X-ray examinations in 11 cases; it occurred after intervals 1–5 years in eight other cases and the Kveim test was positive in another one. In two patients the disease was still confined to the central nervous system at the time of the last follow-up. Histological proof was obtained by biopsy from a lesion in 16 cases and from a Kveim test in 16. There was no histology in five cases in which the diagnosis was supported by strong clinical and cumulative indirect evidence. Neurosarcoidosis frequently runs a benign course with an unpredictable, but sometime gratifying response to steroid therapy. Therefore biopsy of nervous or meningeal tissue is often unjustifiable and actual histological evidence of neurosarcoidosis was only obtained in seven cases.

The principle neurological findings in the two groups are set out in Tables II and III. The predominance of cranial nerve palsies due to basal meningitis is a well known feature of the disease, but diabetes insipidus occurred in only one of our cases and there were no other patients with hypothalamic or pituitary involvement in this series In most cases there were multiple abnormalities, not only because basal meningitis frequently affects many cranial nerves and causes hydrocephalus, but also the parenchymal lesions were often accompanied by meningitic lesions. When multiple lesions occurred without increased intracranial pressure a diagnosis of multiple sclerosis was often suggested and appeared to be confirmed when, as frequently happened, cranial nerve lesions were intermittent.

The radiological examinations performed in these cases and the results are shown in Table IV.

The one abnormal skull X ray showed an erosion of the occipital bone extending into the foramen magnum (Fig.1) which did not change during 18 months follow-up on steroid therapy. This patient was a 42-year-old woman with typical pulmonary and skin lesions and a positive Kveim test. She had multiple cranial nerve palsies and evidence of basal meningitis with hydrocephalus on CAT and pneumoencephalography. The skull lesion was not submitted to biopsy.

The CAT findings are set out in Table V.

In cases 16 and 28 which are discussed later, there was a peripheral intracerebral mass of slightly greater than brain attenuation which enhanced homogeneously (Figs. 2 and 3). Computed tomography showed dilatation of the ventricular system in seven patients.

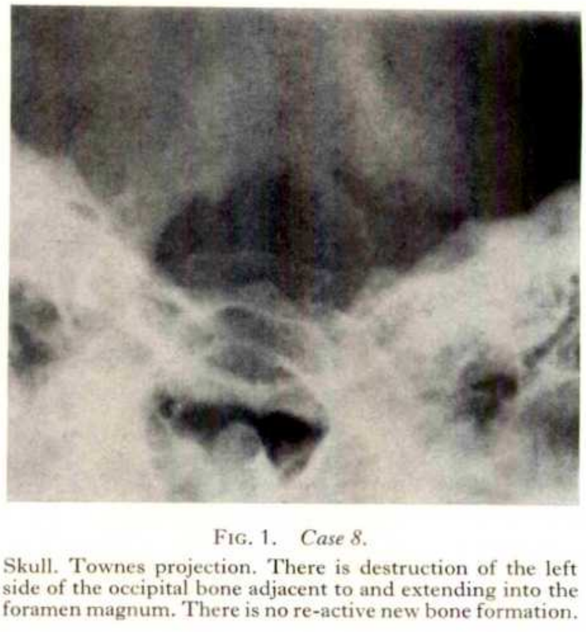

Fig. 1. *Case 8.*

Skull. Townes projection. There is destruction of the left side of the occipital bone adjacent to and extending into the foramen magnum. There is no re-active new bone formation.

TABLE I

Case Group	Age	Sex	Tissue diagnosis	Neurological manifestations	Other manifestations
1A	44	M	Skin biopsy +ve Nerve biopsy +ve	Peripheral neuritis Pseudo bulbar palsy Spastic paraparesis	Skin infiltration
2B	24	F	Kveim +ve	Painful eye movements Optic neuritis	Cervical lymphadenopathy Enlarged peribronchial nodes Episcleritis
3B	37	M	Kveim +ve	Trigeminal neuralgia Blurred vision Retinal vein thrombosis	Choroidoretinitis Hypertension
4A	57	M	Liver biopsy +ve	Sacral nerve root lesions	Mediastinal and hilar adenopathy
‡ 6B	22	M	Node biopsy +ve	Spinal cord lesion—probably ischaemic	Generalized lymphadenopathy hepatomegaly
7B	33*	F	Kveim +ve	Bilateral facial palsy	Bilateral uveitis Bilateral hilar ademopathy Pulmonary infiltration
8A	35	F	Kveim +ve	Multiple cranial nerve palsies	Skin infiltration
9A	30	F	Kveim +ve	Paraesthesia Blurred vision Ataxia	Nasopharyngeal sarcoid (1963) Mediastinal hilar nodes 1963–70 Chest clear 1975
10A	54	M	Scalene node biopsy +ve Liver biopsy +ve	Dysphagia Multiple cranial nerve palsies	Liver involvement Skin lesions, uveitis
11B	51	F		Multiple cranial palsies, ataxia, headache, dysartria, chronic papilloedema	Retinopathy, hypercalcaemia, Febrile episodes, uveitis Mantoux −ve
12A	22	F	Kveim +ve	Multiple cranial nerve palsies. Weakness L. arm	Erythema nodosum Hilar nodes 61—clear 75
13A	37	F		Headache, multiple cranial nerve palsies	Erythema nodosum Enlarged hilar nodes which regressed in 2/12
14B	32	F	Node biopsy +ve	Spastic paraparesis	Hilar mediastinal adenopathy Pulmonary fibrosis
15B	30	M	Meningeal biopsy outlet IVth ventricle +ve Kveim +ve	Headache, epilepsy, confusion	Nil
16B	24†	F	Mediastinal node biopsy +ve	Headache, diplopia, seizures, paraparesis	Enlarged hilar and mediastinal nodes Enlarged axillary nodes
17B	44	F	Kveim +ve	Headache, giddiness, diabetes insipidus, diplopia	Enlarged hilar and mediastinal nodes two years
18B	35	F	Kveim +ve Nerve biopsy +ve	Bilateral facial palsy, papilloaedema	Hilar lymphadenopathy one year
19B	40	F		L. paraesthesia, quadriparesis, multiple cranial nerve palsies CSF lymphocytes 200 Improved with steroids	Nil
20B	47	F	Kveim +ve	Multiple cranial palsies	Nil
21B	62	M	Kveim −ve	Headache, confusion, cranial nerve palsies, peripheral neuritis (on steroid therapy)	Skin infiltration
22B	37	M	Kveim +ve	Dysphagia, dysarthria Bilateral VII nerve palsy	Nil
23B	66	M		R. VII nerve palsy R. Deafness (conductive)	Uveitis, bilateral parotid gland enlargement
‡ 25A	31	F	Liver and scalene node biopsy +ve	R. hemisphere signs L. VII nerve palsy	Hilar adenopathy (1963) Fibrosis and Bullae both lungs (1972)
26B	27†	M	Kveim +ve	R. VII Nerve palsy	Uveitis
27B	29	F		Epilepsy	Hilar and mediastinal adenopathy
28A	34*	M	Kveim +ve Skin biopsy +ve Mediastinal node +ve Cerebrum +ve	Headaches, seizures R. hemisphere signs Mental changes	Hilar and mediastinal lymph-adenopathy. Skin infiltration

(*Continued on next page*)

TABLE I (*continued*)

Case Group	Age	Sex	Tissue diagnosis	Neurological manifestations	Other manifestations
29B	27	M	Kveim +ve Meningeal biopsy from suprasellar cisterns +ve	Headaches, multiple cranial nerve palsies, dysarthria, spastic paraparesis Lymphocytic meningitis	Recurrent pyrexia
30A	34†	F	Kveim +ve Cervical node +ve	Headaches with confusion, papilloaedema, ataxia, epilepsy, cranial nerve palsies	Bilateral hilar adenopathy Cervical lymphadenopathy
31B	38	F	Spinal cord +ve Node biopsy +ve	Parasthesia, Paraparesis	Hilar and mediastinal adenopathy
32B	62†	F	Node biopsy +ve	Headache, loss of vision	Hilar and mediastinal adenopathy progressing to lung infiltration Cervical lymphadenopathy
33B	29	M	Liver biopsy +ve	Multiple cranial nerve palsies, L. L. hemiparesis	Bilateral hilar lymphadenopathy
34B	27	M	Kveim +ve Meninges posterior fossa +ve Cerebellum +ve	Headache, papilloedema, confusion, seizures, dysarthria, multiple cranial nerve palsies.	Sarcoidosis in branchail cyst

* = Guyanian Indian
† = West Indian
‡ = Cases 5 and 24 were excluded because evidence of the nature of neurological disease on review was considered to be inconclusive.

TABLE II

	Group A	Group B
Cranial nerve lesions	7	18
Diabetes insipidus	0	1
Hemisphere signs	3	3
Seizures	2	4
Confusion, dementia	1	3
Headache plus other signs	3	9
Dysphagia, dysarthria, ataxia	3	3
Cord lesion	2	6
Sacral nerve root lesion	1	0

TABLE III

Cranial nerve involved	Number of palsies		
	Group A	Group B	Total
1	0	2	2
2	2	4	6
3	2	6	8
4	2	0	2
5	4	4	8
6	3	5	8
7	3	13	16
8	2	3	5
9	2	1	3
10	2	0	2
11	3	0	3
12	2	3	5
Total number of palsies	27	41	68
Number of patients affected	7	18	25

No cranial nerve palsy in seven cases only.
Single cranial nerve palsy in five cases only.
Multiple cranial nerve palsies in 20 cases.

TABLE IV

Investigation	Group A	Group B	Abnormal
Skull X rays	10	22	1 (3%)
Spine X rays	5	5	0 (0%)
Isotope scan	3	8	0 (0%)
CAT	6	7	10 (77%)
Air studies	3	7	4 (40%)
Angiography	3	9	3 (25%)
Myelography	1	6	2 (29%)

In two of these, including a patient (Case 16) described in detail below, there was enhancement of the basal meninges suggesting active granulomatous infiltration. This was also present in one case in which CAT was normal prior to enhancement. In seven other cases, including three with ventricular dilatation, there was no enhancement (Fig. 5). In two of these pneumo-encephalography and ventriculography showed obstruction of the outlets of the fourth ventricle (Fig. 4) due to adhesions which were confirmed at surgery. In another patient pneumo-encephalography showed absent filling of the suprasellar cisterns which was also due to arachnoiditis (Fig. 6). In these cases it is presumed that the disease is less active or perhaps fibrotic so that enhancement which is due to active granulation tissue and increased vascularity does not occur. However, the time between onset of neurological symptoms and scanning in the enhancing group (two months, two years and two years) was straddled by the group which did not enhance (six weeks, two months, two

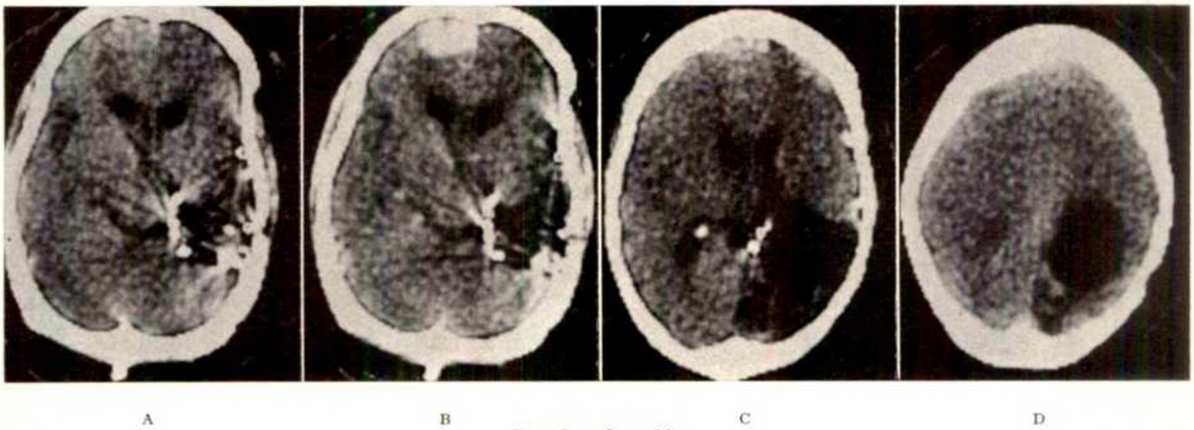

FIG. 2. *Case 28.*

(A) Before and (B) after intravenous contrast medium. There is a left fronto-polar mass of slightly increased attenuation which enhances homogeneously. There is low attenuation in the middle and posterior parts of the right temporal lobe due to brain damage associated with a previous sarcoid granuloma and its removal. (C) And (D) higher cuts showing low attenuation in the right parietal and occipital lobe with porencephalic cyst formation following infarction subsequent to the previous surgery.

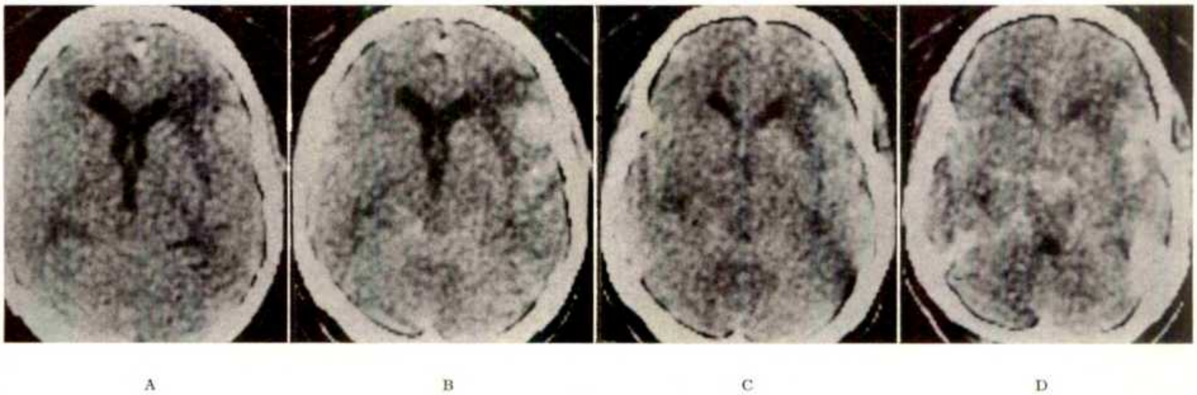

FIG. 3.

(A) Plain. (B) Following intravenous contrast. There is a small mass of slightly increased attenuation in the right frontal lobe adjacent to the convexity which enhances homogeneously. There is surrounding low attenuation suggesting oedema around the lesion. (C) Before and (D) after intravenous contrast medium. There is enhancement of the basal meninges due to chronic granulomatous meningitis.

TABLE V

Plain CAT		Repeat CAT after intravenous contrast medium			
			Enhancement		
		Contrast given	Mass	Basal meninges	No enhancement
Peripheral mass	2	2	2	1	1
Hydrocephalus	7	4	0	1	3*
Normal plain scan	4	4	0	1	3†
Total	13	10	2	3	7

Air studies showed * obstruction of fourth ventricle foramina in two
† irregular filling of suprasellar cisterns in one

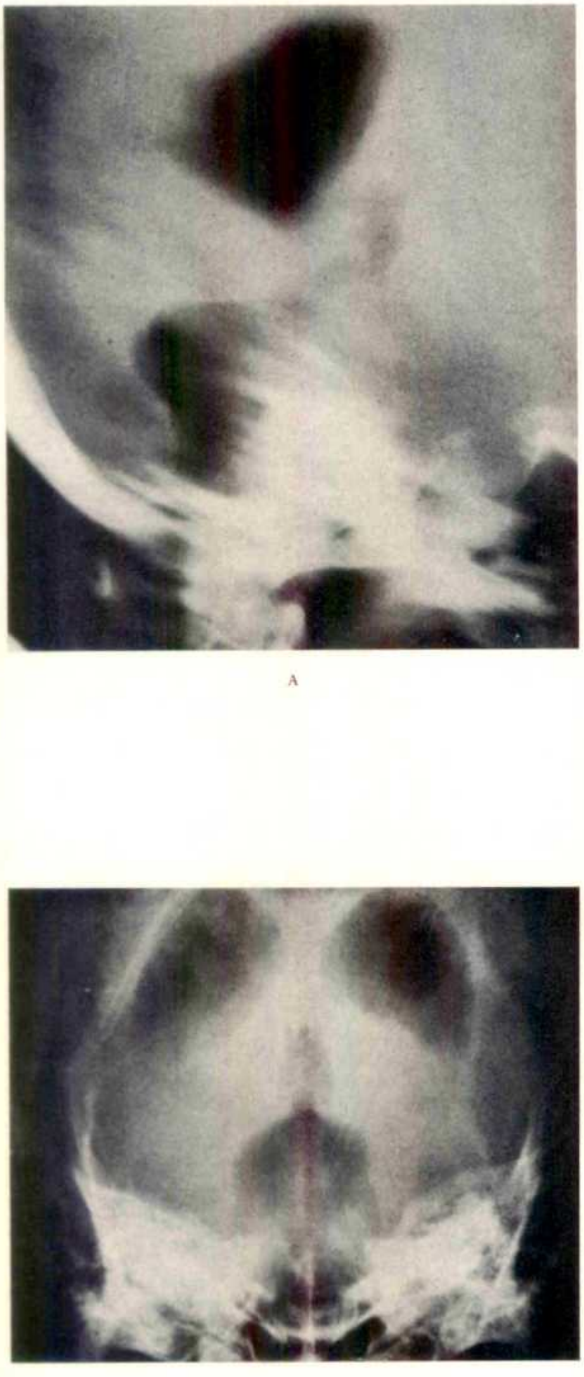

FIG. 4. *Case 30.*

Ventriculogram. Browdown position (A) midline lateral tomogram (B) Reversed Townes projection EMI scan showed dilatation of the whole ventricular system. There was no abnormal enhancement. There is dilatation of the lateral third and fourth ventricles with obstruction of the outlet of the fourth ventricle. This was shown to be due to fibrotic sarcoid granuloma in the meninges.

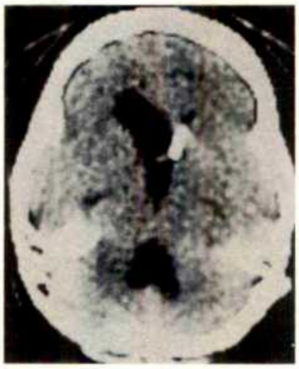

FIG. 5. *Case 30.*

CAT. There is dilatation of the right lateral ventricle and of the third and fourth ventricles. A shunt tube has been introduced into the left lateral ventricle with its tip encroaching on the Foramen of Monro. This ventricle, which was previously dilated, is now normal in size, being adequately drained through the functioning shunt. There was no enhancement of the basal meninges on this or previous scans. The ventricular dilatation could have been due to obstruction at the outlets of the fourth ventricle or in the basal cisterns, the former being confirmed by ventriculography (Fig. 4). The obstruction of the left Foramen of Monro which has developed since the ventriculogram could be due to the position of the shunt tube or adhesions in this region also.

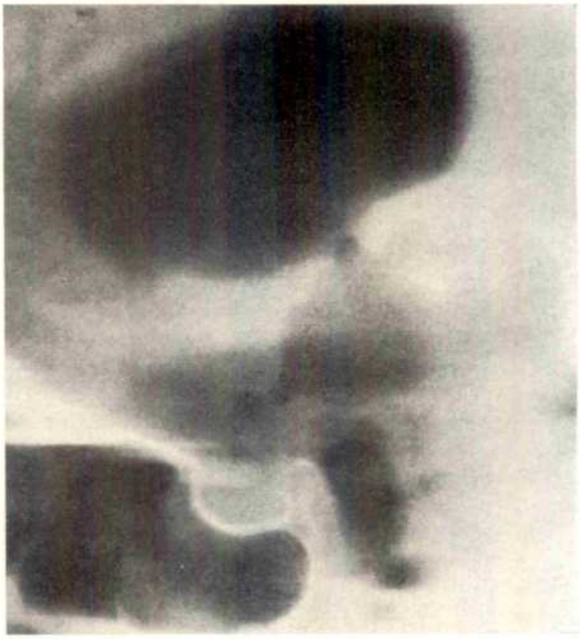

FIG. 6. *Case 29.*

Pneumo-encephalogram. Lateral tomogram. Brow-up position. There is a minor degree of dilatation of the lateral and third ventricles. The anterior recesses of the third ventricle are slightly deformed. There is only a little loculated air in the suprasellar cisterns due to fibrotic meningeal sarcoid.

years, three years, three years and ten years) and meningeal biopsy showed granulomas in fibrotic tissue in two of the cases which did not enhance. Basal adhesions were shown by pneumoencephalography in one further case who did not have a computed tomogram. Six other air studies were normal.

Cerebral angiograms were performed on 12 patients, but were abnormal in only three cases and one of these only showed evidence of lateral ventricular dilatation. The other two cases are of more interest.

Case 28 was a 37-year-old Guyanian Indian male who had known pulmonary and skin lesions of sarcoidosis of three years duration, confirmed by biopsy and a positive Kveim test. He was referred to another neurosurgical unit with a recent history of headache and epilepsy and examination revealed multiple cranial nerve palsies and a mild left hemiparesis. An isotope scan was negative but a right carotid angiogram revealed an avascular mass in the temporal lobe. A mass of sarcoid granuloma was excised by temporal lobectomy, but it was in intimate contact with posterior and middle cerebral cortical branches and parietal lobe infarction followed its removal. Four months later there was recurrence of headache and epilepsy and the patient was then admitted to The National Hospital for Nervous Diseases. CAT (Fig. 2) showed a mass of slightly greater than brain attenuation at the periphery of the left frontal lobe which showed homogeneous enhancement. There was also dilatation of the right lateral ventricle and a parietal porencephalic cyst due to the previous surgery and infarction. The patient showed little clinical improvement despite a five-month course of intensive steroid therapy and follow-up CATs were unchanged.

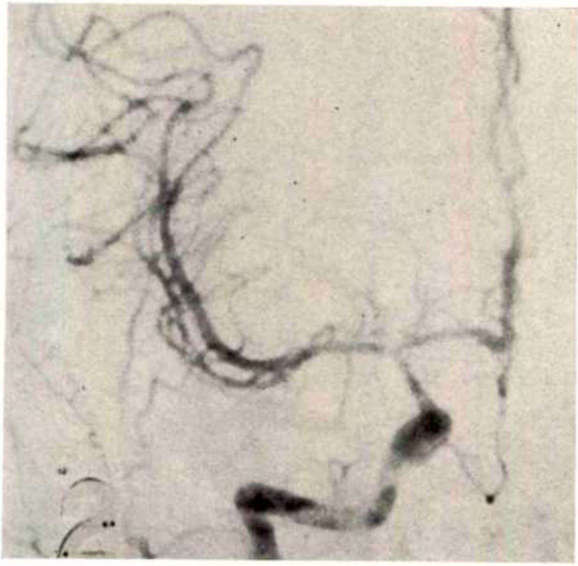

FIG. 7. *Case 19.*

Right carotid angiogram. Subtraction print. A.P. projection arterial phase. There is narrowing of the supraclinoid part of the right internal carotid and of the origin of the middle and to a minor degree of the anterior cerebral arteries.

Case 19 was a 41-year-old white female who presented with a lymphocytic meningitis (CSF lymphocytes 131 ml: protein 200 mg/ml: glucose 23 mg/ml), paralysis of right seventh and eighth cranial nerves and paraparesis. There was smooth narrowing of the termination of the right internal carotid artery and origin of the middle cerebral arteries (Fig. 7). The pneumo-encephalogram showed no abnormality. The visual evoked responses were abnormal. Multiple sclerosis was considered, but the angiographic and CSF findings were not in favour of this diagnosis. Tests for tuberculosis and other organisms were negative. On treatment with Prednisone and anti-tuberculous therapy, the CSF returned slowly to normal over a period of two years, but the neurological disability remained unchanged over a seven-year follow-up. There has been no evidence of systemic sarcoidosis and no histological evidence has been obtained. The present diagnosis is sacoidosis; though this is likely it must still be considered subjudice.

Myelography was performed in five of the eight patients with cord lesions. It was normal in three of these and in the patient with sacral root involvement; it was not performed in the three other cases because the disability caused by the spinal lesion was slight. All these cases had histologically proven sarcoidosis. The other two cases both had swellings of the spinal cord. Case 16 was a 24-year-old West Indian female who presented with head and neck ache, vomiting, convulsions and paraparesis. Examination revealed papilloedema and enlarged hilar lymph nodes and a cervical node biopsy confirmed sarcoidosis. Computed tomography (Fig. 3) showed a peripheral right fronto-temporal mass of greater attenuation than adjacent brain which enhanced homogeneously and there was also enhancement of basal meninges. Myelography using Metrizamide by the lateral cervical route showed arachnoiditis in the lower cervical and upper dorsal region with slight swelling of the upper dorsal cord (Fig. 8). There was complete obstruction in the lower dorsal region. The symptoms gradually improved on steroid therapy and CAT showed resolution of the parenchymal lesion (Fig. 9),

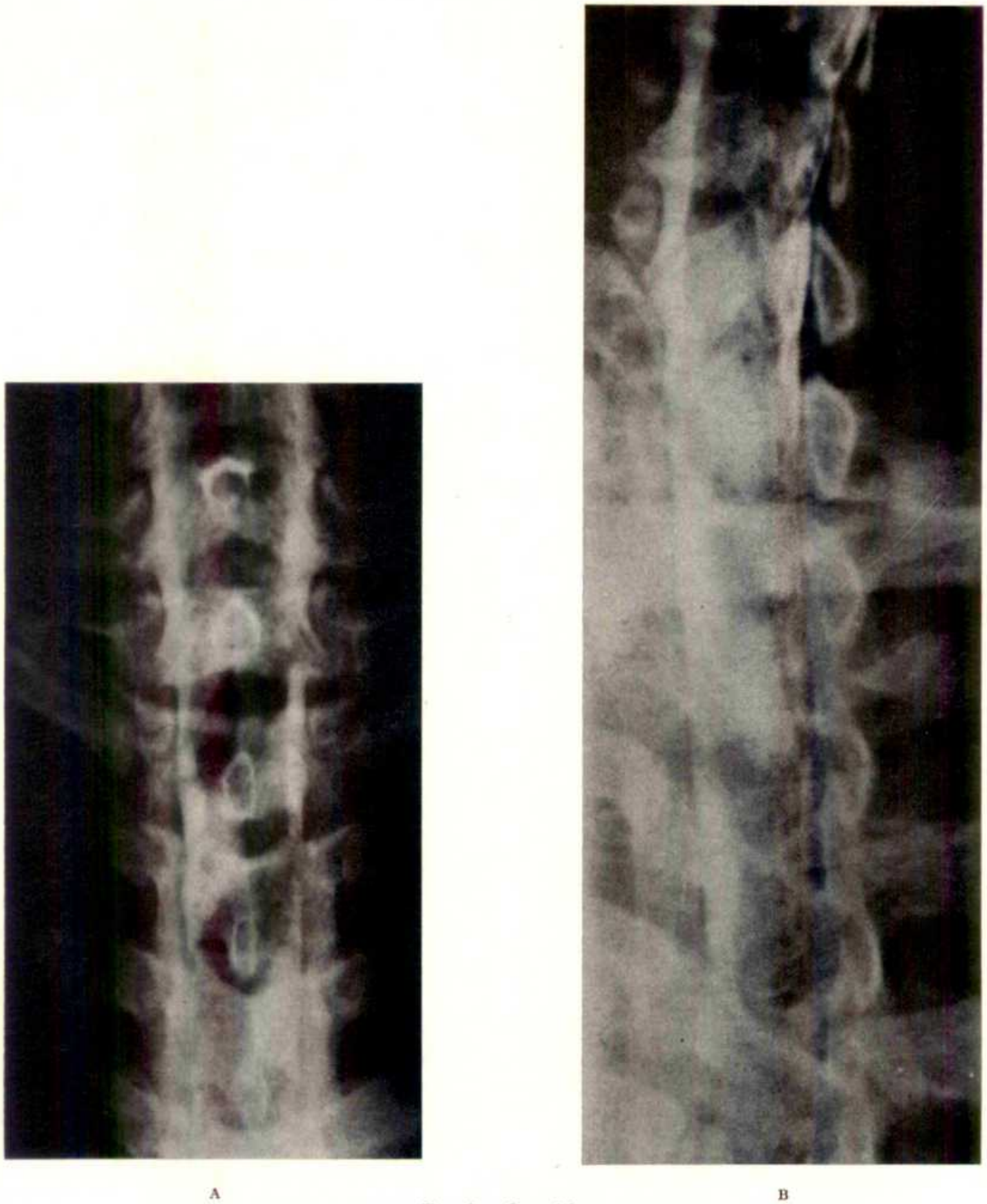

FIG. 8. *Case 16.*
Metrizamide myelogram. (A) A.P.
(B) Oblique projections.
There is slight swelling of the upper dorsal and cervico-dorsal part of the spinal cord with irregular filling of the subarachnoid space suggesting arachnoiditis. There is complete obstruction in the lower dorsal region.

but the basal meninges continued to enhance (Fig. 10.)

Case 31 was a 38-year-old white female who presented to another neurosurgical unit with paraparesis. Examination revealed enlarged hilar and cervical nodes and a biopsy confirmed sarcoidosis. Myelography showed swelling of the cervical cord (Fig. 11) which was confirmed at surgical exploration to be due to an infiltrating intramedullary mass and by histology to contain typical sarcoid granulomata. The patient was transferred to The National

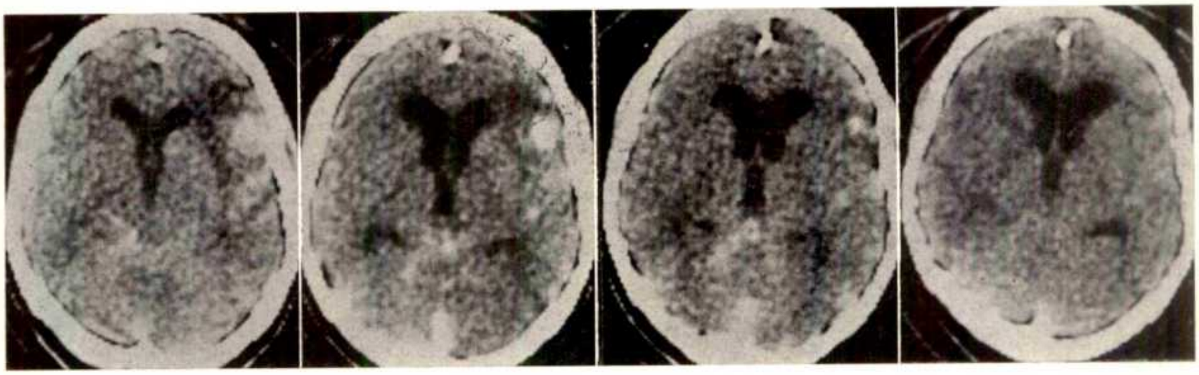

FIG. 9. *Case 16.*

Computed axial tomograms following intravenous contrast medium showing progressive clearing of the peripheral right frontal lesion over a period of nine months. There has been dilatation of the lateral ventricles over the time of observation.

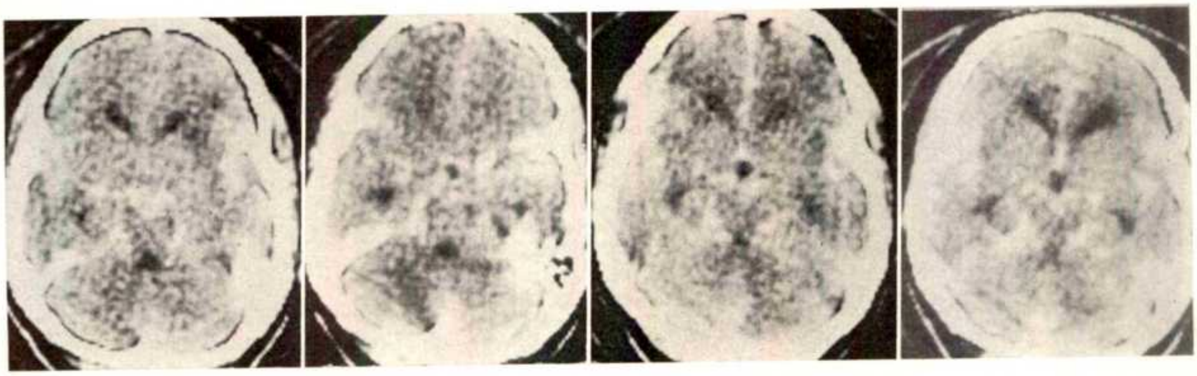

FIG. 10. *Case 16.*

Computed tomograms following intravenous contrast medium. Same cut repeated during therapy. The enhancement of the meninges persists unchanged.

Hospital for Nervous Diseases, where re-screening showed persistance of the cervical cord swelling. The paraparesis resolved on high dosage steroid therapy over the subsequent three months.

DISCUSSION

The predominance of females and young adults and the relatively high number of Negroes in our series is typical: Guyanian Indians have not been previously noted to have an increased susceptibility to sarcoidosis, but the presence of two in our series is probably not a coincidence.

The cerebral presentations in our cases differ from previous series in the lower incidence of lesions of the hypophysis and optic nerves (Schuber *et al.*, 1971; Hankinson and Banna, 1976) and of the hypothalamus (Colover, 1948).

Erosive skull lesions with no reactive bone formation have only been previously recorded in four cases of sarcoidosis (Olsen, 1963). An increased incidence of tuberculosis is well known in sarcoid cases and the skull lesion should be biopsied if histological evidence has not been obtained, or if there is unexpected progression on steroid therapy. The very low positive yield from skull X-rays suggests that they are not necessary as a routine investigation in these cases. Calcification has been described as a rare occurrence in parenchymal sarcoid lesions (Herring and Urich, 1969), but this is much more readily shown on CAT and bone erosion may also be identified at appropriate window levels.

Isotope scans were negative in 11 cases, including both those with intracerebral masses, the others having basal meningitis, hemisphere signs or seizures. It is evident that isotope scans are not of value in excluding sarcoid masses and since the uptake of isotope is not specific for any pathology they are not of value in differential diagnosis. They are no longer indicated in the elucidation of these cases.

Computed tomography is the most informative cranial neuroradiological study. As would be expected the non-caseating granulomas show as slightly high-attenuation, homogeneously enhancing mass lesions, with little surrounding low attenuation, which in our experience, are peripherally situated. Similar appearances may occur with other pathologies but most of those which complicate sarcoidosis cause easily distinguished abnormalities. Infarction is usually of low attenuation and enhancement occurs for only a limited period. Other inflammatory lesions causing clinical syndromes similar to sarcoidosis may necrose and show central low attenuation or calcification though some granulomas, including tuberculomas, may be identical; careful examination of the CSF may be helpful but many clinicians consider that anti-tuberculous chemotherapy should be given to all sarcoidoses with cerebral lesions because of the difficulty in excluding super-added TB.

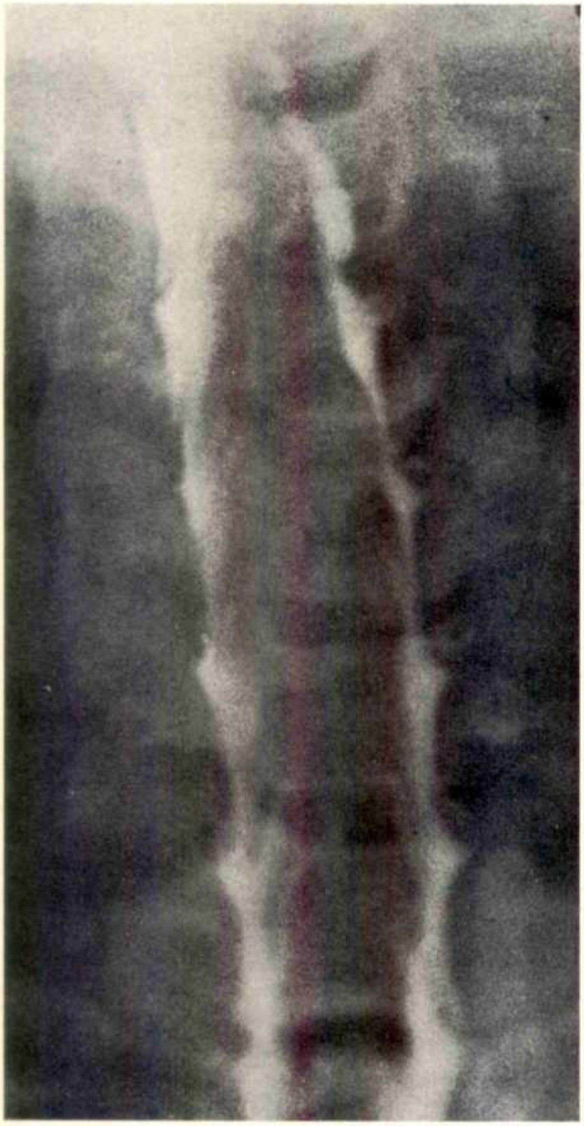

Fig. 11. *Case 31.*

Myodil myelogram. P.A. projection. There is increase in the transverse diameter of the mid and lower parts of the cervical cord due to intramedullary swelling.

The onset of severe neurological symptoms in patients with known sarcoidosis may also be due to invasion by opportunistic organisms including various fungi and papova viruses, which cause progressive multifocal leuko-encephalopathy (PML). In contrast to granulomas, PML is confined to white matter, usually affecting the cerebral hemispheres (Carroll *et al.*, 1977). It causes low attenuation masses which occasionally show central enhancement. The lesions are usually progressive, but remissions do occur (Bosch *et al.*, 1976).

Basal arachnoiditis causing enhancement on CAT has been shown in chronic infective meningitis and in neoplastic meningitis (Enzmann *et al.*, 1976). Usually the clinical laboratory tests allow easy distinction from sarcoidosis but it should be noted that tuberculous meningitis has been described in association with sarcoidosis (Hopkins, 1973).

The combination of clinical and/or CAT evidence of multiple lesions within the brain, spinal cord or meninges may be taken as strong presumptive evidence that all the lesions are due to sarcoidosis without further study in cases with systemic sarcoidosis. Hydrocephalus is best diagnosed by CAT and enhancement of the basal meninges is confirmatory evidence of the site of obstruction being at the base and that the granulations are active. In absence of enhancement the process may be fibrotic and the site of the lesion causing hydrocephalus may not be evident on CAT alone. In these cases air studies will show the site of obstruction and failure of filling of cisterns may give some confirmation of the position of adhesions. It is debatable whether such studies are still indicated when CAT is available if the symptoms are due to hydrocephalus alone, but they are of value if a mass lesion needs to be excluded in cases with optic nerve or chiasmal compression.

The non-invasiveness of CAT allows careful follow-up of intracranial lesions so that progress can be monitored and, even if the diagnosis of any particular lesion is uncertain, surgery may be held in reserve to be used if there is unexpected increase in the size of a mass or progressive hydrocephalus. Thus, in one of our cases an intracerebral lesion totally disappeared on steroid therapy (Fig. 9). Only one case with basal meningeal enhancement was followed with appropriate scans over a period of 15 months; there was no change.

The relatively higher incidence of neuro-sarcoidosis in autopsy as compared with clinical series (Ricker and Clark, 1962) suggests that more cases may be discovered if patients with vague symptoms, which could possibly be due to intracranial involvement, are subjected to computed tomography. However, we performed CAT on three further cases with iridocyclitis and headache, without any signs of an intracranial lesion and all these were entirely normal.

Cerebral angiography has nothing to contribute to diagnosis if CAT is available, unless an appearance suggesting an incidental tumour, which could have a pathological circulation, is shown. Sarcoid masses are avascular and similar to other avascular masses of any aetiology (Saltzman, 1958; Thompson, 1961). Histological studies have demonstrated involvement of the adventitia and media of smaller cerebral arteries by sarcoid granulation tissue which sometimes causes narrowing of the lumen (Meyer *et al.*, 1953). It is well known that meningitis due to granulomatous or pyogenic inflammation can cause narrowing of basal vessels, but these vessels have never been shown to be compromised in sarcoidosis (Herring and Urich, 1969). Unfortunately histological proof of the diagnosis is lacking in our case and even in a young woman with a clinical syndrome confidently diagnosed as sarcoidosis, the narrowing is insufficient evidence of involvement or compression of the vessel wall by sarcoid granuloma.

Sarcoidosis involving the spinal cord has been recently reviewed by Nathan *et al.* (1976). Including their cases there are apparently 11 cases in the literature with proved histology. In both our cases the diagnosis of systemic sarcoidosis was firmly established but in only one of them was exploration of the spinal cord and biopsy performed. In the other case the combination of spinal and basal arachnoiditis, cord swelling and a superficial cerebral mass lesion, which was followed to complete resolution with CAT during steroid therapy, leaves no doubt about the nature of the cord lesion. In both these patients the cord symptoms improved during steroid therapy. Cord involvement may be due to sarcoid vascular lesions as well as to intramedullary granulomas or meningeal involvement and the precise aetiology of cord involvement in our three cases without myelographic abnormality and the three others in which myelography was not performed has not been established. Myelography is only indicated if a cord lesion other than sarcoidosis is suspected or if local surgery is contemplated should an amenable lesion be shown. Myelographic changes in neurosarcoidosis are not specific and the diagnosis can only be suspected in the presence of suggestive intracranial lesions or when sarcoidosis is present in other systems.

The disappointingly large number of negative radiological investigations in these patients with neurological lesions and sarcoidosis should be viewed in the knowledge that in over two thirds of them the diagnosis of sarcoidosis was only established at the time of neurological presentation, often after neuro-radiological studies had been performed. In other cases such studies were performed to exclude a second pathology at a time before CAT was available. The advantages of the latter in the elucidation of cerebral lesions is evident; only uncommonly does it need to be supplemented by further contrast studies in patients with known sarcoidosis.

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Book review

Advances in Neurosurgery—4. Lumbar Disc. Adult Hydrocephalus. Edited by R. Wüllenweber, M. Brock, J. Hamer, and M. Klinger, (Berlin, Heidelberg, New York, Springer-Verlag), pp. xxiii+338, illus., 1977. DM76.00.

This book contains the proceedings of the 27th Annual Meeting of the Deutsche Gesellschaft für Neurochirurgie, September 1976. No new developments of radiological interest are recorded on either of the main topics, but the section on adult hydrocephalus is largely concerned with the pathophysiology and diagnosis of normal pressure hydrocephalus, including the abnormalities revealed by computed tomography and cisternography and the place of these investigations in this difficult subject.

A few of the communications are specifically concerned with radiology. These include a study controlled by CT of the effect of dexamethazone and frusomide on peritumoral oedema, the use of biplane simultaneous angiotomography for the analysis of intracranial aneurysms and experimental work on discography with water and oil soluble contrast media in rabbits.

Though neuroradiologists may wish to study the papers which have been mentioned, the great majority of the communications are not of radiological interest.

B. E. KENDALL.

1978, *British Journal of Radiology*, *51*, 93–98 FEBRUARY 1978

The "mandibular mantle"—a sign of rickets in very low birth weight infants

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ABSTRACT

Mandibular periosteal new bone formation (the "mandibular mantle") is described in very low birth weight infants with other signs of severe metabolic bone disease. In infants with onset of dyspnoea and apnoea, between two and three months of age, this mandibular change suggests that the lung disorder is of skeletal, rather than pulmonary origin and aids in differentiation therefore, from the Mikity-Wilson Syndrome (pulmonary dysmaturity).

The cardinal radiological features of nutritional rickets are well known (Caffey, 1973). A feature which we have not seen recorded previously, is symmetrical periosteal new bone formation on the inferior aspect of the mandible. The present paper describes this change in five low birth weight infants who developed severe nutritional rickets before three months of age.

CLINICAL DETAILS

Four of the infants were males. All were born between 28 and 31 weeks gestation and had very low birth weights, from 0.64 kg to 1.80 kg (Table I).

Each of the pregnancies had been complicated, but only patient 4 was asphyxiated at birth; mild idiopathic respiratory distress syndrome (IRDS) developed in patient 5. Between five and ten weeks of age, patients 2–5 developed insidious onset of dyspnoea with sub-costal recession and episodes of apnoea. Patient 1 was being investigated for mild obstructive jaundice when at 13 weeks of age, he had a series of generalized seizures associated with hypocalcaemia and hypomagnesaemia. At about the same time, he also developed wheeze and dyspnoea. Overt clinical features of rickets were however only present in patient 2, who had rachitic expansion of the wrists and a large anterior fontanelle. Each of the babies was receiving supplements of vitamin D; in patient 1, this was 5 μg, patient 2, 10 μg, and patients 3–5, 20 μg daily.

BIOCHEMISTRY

At the diagnosis of bone disease the following changes were found (Table II). Three infants were hypocalcaemic, two of whom were also hypophosphataemic and hypomagnesaemic. Each of the latter children had generalized aminoaciduria and patient 3 who had the lowest serum calcium of all, had tyrosinuria. The alkaline phosphatase was elevated in all the infants. This was almost entirely of osteoblastic origin, as shown by isoenzyme separation on polyacrylamide gel. Subclinical icterus was present in patients 1–4; highest values were found in patient 1, whose total and direct reacting bilirubins were 108 and 82 μmol/l, respectively.

TABLE I

CLINICAL FEATURES OF INFANTS

Patient	Sex	Birth weight (kg)	Gestational maturity (wk)	Pregnancy	Apgar score (1 min)
1	M	1.80	31	Placenta praevia, caesarian section	9
2	M	0.83	28	Anterpatum haemorrhage	gasped at birth
3(died)	M	0.71	30	Pre-eclampsia	8
4	M	1.45	30	Severe pre-eclampsia, caesarian section	6
5(died)	F	0.64	29	Antepartum haemorrhage	8

TABLE II

BIOCHEMISTRY AT DIAGNOSIS OF BONE DISEASE

Patient	Calcium (m mol/l)	Magnesium (m mol/l)	Inorganic phosphate (m mol/l)	Alkaline phosphatase (KA units)	Urinary amino acids
1	1.65	0.51	1.26	66	generalized rise
2	1.80	0.57	1.29	55	generalized rise
3	1.43	1.14	2.33	47	tyrosinuria
4	2.39	—	2.02	338 IU	normal
5	2.48	0.74	2.50	300 IU	threoninuria

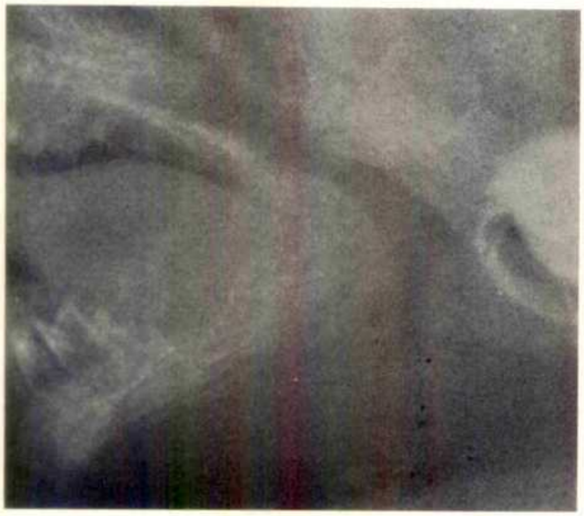

FIG. 1.

Patient 3, aged five weeks. Lateral view of mandible showing fine layer of periosteal new bone formation on inferior surfaces of horizontal rami.

Values for plasma proteins, full blood picture, including total and differential white blood counts were normal for age.

RADIOLOGY

The findings are similar in each, and are described together.

Skull and facial bones

There was marked demineralization of the vault, with poorly defined sutures and sharply etched inner ear structures. A clearly defined layer of periosteal new bone was present along the inferior border of the mandible—the 'mandibular mantle" (Fig. 1). This was best developed in patients 1 and 2, in whom it extended up the lateral margins of the ascending rami (Fig. 2). In patient 2 this persisted for about ten weeks, gradually consolidating and finally merging with the cortex of the mandible. Follow-up showed no residual abnormality.

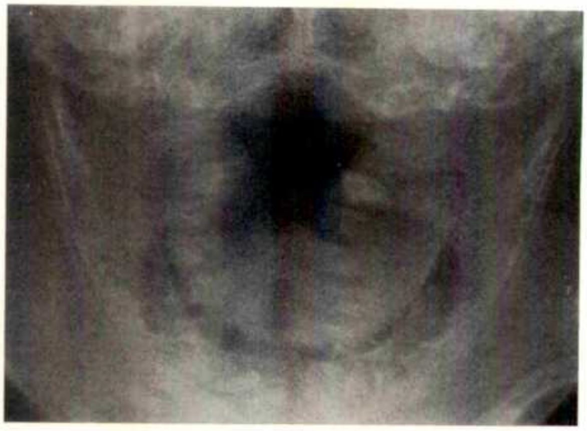

FIG. 2.

Patient 1, aged 13 weeks. A.P. view of mandible showing well defined layer of periosteal new bone extending up outer aspects of ascending rami.

Long bones

The principal findings were demineralization and periosteal new bone formation along the shafts. These changes were most pronounced in patient 2, in whom there were also fractures of both lower radial, ulnar and tibial shafts and each mid-fibula (Fig. 3). In patients 2, 3 and 5, metaphyseal cupping and splaying were present (Fig. 4); these findings were not seen in patients 1 or 4. There was no X ray evidence of hyperparathyroidism in any patient.

Chest

In patients 2, 3 and 5, the lungs showed features suggestive of early Mikity-Wilson syndrome (MWS). These consisted of over-inflation and linear strands; in patient 2, there were also cystic changes in the right lower zone. Over-inflation *per se* was present in patient 1 and all five infants had areas of patchy collapse/consolidation (Fig. 5). In the immediate neonatal period, patient 4 showed changes of moderately severe IRDS, but the lungs had

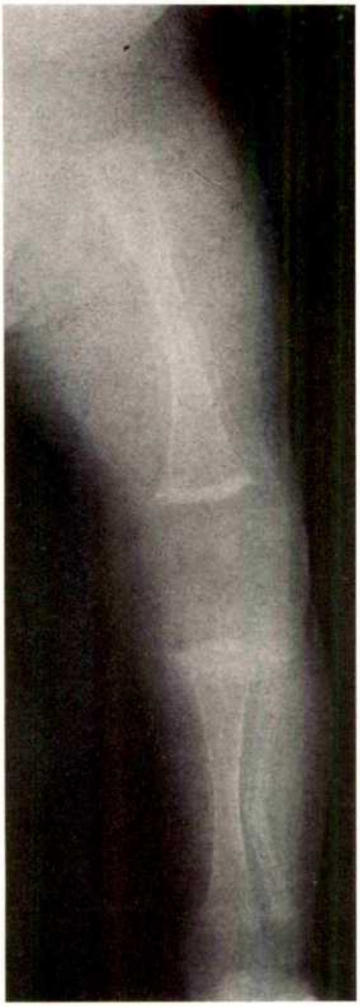

FIG. 3.

Patient 2, aged ten weeks. A.P. view of leg showing periosteal new bone formation on the shafts of the long bones, a healing fracture of the fibula, generalized demineralization with absence of ossification centres at the knee and slight metaphyseal splaying.

cleared by the time skeletal demineralization had developed.

The rib cage was demineralized in all patients. Multiple fresh and healing rib fractures of the lateral arcs of the middle ribs were present in patients 1 and 2 associated with extensive periosteal new bone formation. In patients 1 to 4, there was splaying of the anterior rib ends. Concavity and irregularity of the inferior scapular angles, typical of rickets, were present in patients 1 and 2.

Spine

Gross demineralization was present in each of the infants. In patient 1, who has been reported previously (Thomas and Glasgow, 1974), this affected the axial more than the appendicular skeleton.

COURSE

The patients were treated in a variety of ways. Three patients received vitamin D. This was given orally in patients 1 and 3 (30 μg daily) and in patient 2 two large parenteral injections each of 110 μg. Bone disease in patient 4 healed spontaneously and patient 5 was given oral 1α-hydroxyvitamin D* 0.2 μg daily. Respiratory distress became increasingly severe in this infant and also in patient 3. Patient 5 died of respiratory insufficiency in spite of intensive care and ventilatory support. Patient 3 developed paralytic ileus and also succumbed. At necropsy, although the lungs showed patchy pneumonitis, the skeleton was markedly demineralized with changes of osteomalacic bone disease (Glasgow and Thomas, 1977).

DISCUSSION

Nutritional rickets is rare among Caucasian children in the United Kingdom. During the past five years, we have observed osteomalacic bone disease in an increasing number of very low birth weight (VLBW) infants (Glasgow and Thomas, 1977). In the majority, the biochemical and radiological findings were those commonly found in rickets (Caffey, 1973). A few had X ray features in the scapulae (Weiss, 1971).

The particular radiological change seen in the mandible of our five infants has not been reported previously in metabolic bone disease. This was bilateral and symmetrical in distribution and was not associated with abnormality in either haematollogical, bacteriological or serological studies which might have supported an infective aetiology. Subsequently, complete resolution occurred.

Although mandibular thickening most often suggests infantile cortical hyperostosis (Caffey and Silverman, 1945), the presence of rickets, demineralization and fractures made this diagnosis untenable (Table III). Moreover, as rickets healed, the mandibular change regressed.

Periosteal new bone, confined to the long bones, occurs in about 30% of normal mature and preterm neonates (Shopfner, 1966). We have observed this also in preterm infants, some of whom had mild rickets. Earlier French literature described similar changes, frequently associated with jaundice and widespread osteomalacia (Rossier *et al.*, 1958); Boissière *et al.*, 1964). More recently, florid periosteal new bone formation has been reported in

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*Leo Laboratories Ltd., Hayes, Middlesex.

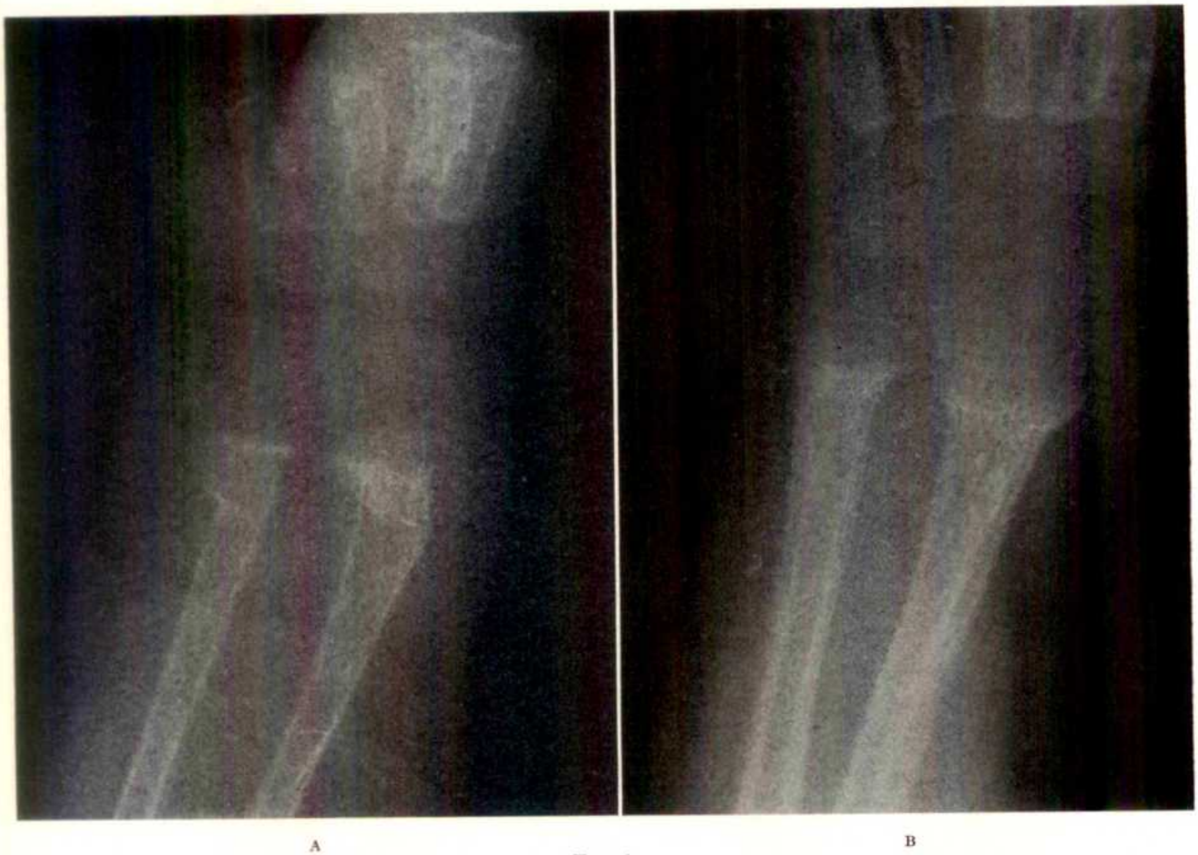

Fig. 4.

Patient 2 left wrist (A) at ten weeks showing demineralization and fractures, (B) at 19 weeks showing changes of healing rickets, with cupping and splaying of metaphyses of radius and ulna and consolidating periosteal new bone.

infants with biochemical changes attributed to copper deficiency (Griscom *et al.*, 1971). None of these features were present in our patients.

Mandibular periosteal new bone was present only in those VLBW infants with most marked bone disease. Although the pathogenesis of this change is not understood, it may be related to the nature of the periosteum in the fetus and preterm infant. Here the periosteum consists of a relatively thick layer of osteoblasts adjacent to the bone cortex. In the presence of severe rickets, there is production of excess periosteal osteoid which calcifies first in its outer layers, rather than from the cortical surface. It may be this pattern of calcification which gives the

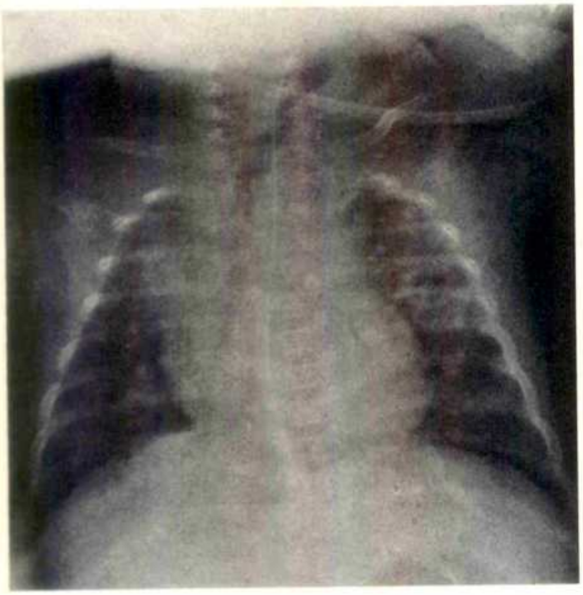

Fig. 5.

Patient 5, aged eight weeks. A.P. chest showing areas of patchy opacity in both lungs, mainly in the mid and upper zones with areas of hyper-aeration.

TABLE III

RADIOLOGICAL FEATURES OF BONE DISEASE

Patient	Age at diagnosis of bone disease (wk)	Mandibular periosteal new bone	Skeleton			Lungs		
			Demineralization	Rickets	Fractures	Consolidation	Over-inflation	Cysts
1	13	+	axial	+	ribs	+	+	—
2	10	+	generalized	+	ribs and long bones	+	+	+
3	5	+	generalized	+	none	+	+	—
4	5	+	generalized	+	none	—	—	—
5	6	+	generalized	+	none	+	+	—

characteristic radiographic appearance, which might be described as a "mandibular mantle".

The presence of this mandibular sign can provide an important diagnostic clue in VLBW infants who develop late onset dyspnoea with apnoeic attacks. Early radiological findings in the MWS are frequently inconclusive, and when these ill-defined lung changes are associated with the "mandibular mantle" the primary lesion is likely to be skeletal rather than pulmonary. Hence the inclusion of a lateral view of mandible in chest radiographs of infants thought to be developing MWS may be of diagnostic value (Glasgow and Thomas, 1977).

Rickets is probably more common in VLBW infants than is generally realized (Glasgow and Thomas, 1977). During the first three months of life, Hillman and Haddad (1975) have shown that preterm infants have low levels of circulating 25-hydroxyvitamin D (25-OHD). A number of factors probably contribute to this, including the concentration of 25-OHD in the maternal circulation at delivery (Rosen *et al.*, 1974). Storage of vitamin D and 25-OHD might be reduced in the newborn infant because of the small amount of muscle and fat. In the adult, 25-OHD is stored in muscle and many other tissues (Mawer and Schaefer, 1969) while vitamin D is deposited in fat (Rosenstreich *et al.*, 1971).

Small babies tend to ingest very small quantities of vitamin D fortified milks (0.01–0.025 μg/dl) and this of itself may occasionally lead to rickets (Lewin *et al.*, 1971). Intestinal absorption of the vitamin may be poor because of profoundly low levels of duodenal bile acid during digestion for the first few weeks of life in VLBW infants (Katz and Hamilton, 1974). Moreover, 25-hydroxylation by the liver is probably markedly impaired (Hillman and Haddad, 1975) and much evidence of the liver's immaturity exists at this age (Lucey, 1960; Rosenberg and Scriver, 1974). On the other hand, utilization might be increased (Nitowsky, 1968).

In view of these impediments, it seems likely that the renal hormone, 1,25-dihydroxyvitamin D is also low and neonatal calcium absorption faulty. Shaw (1976) has shown that accumulation of calcium by the VLBW infant is less than 40% of that by the fetus during the last trimester of pregnancy. During this period, the fetus acquires about 80% of the 25 g of calcium contained within the skeleton of the mature newborn (McCance and Widdowson, 1961). Hence adverse factors which lower the infant's 1,25-dihydroxyvitamin D level compound those inherent in premature delivery.

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Book review

X-rays: more harm than good? By Priscilla W. Laws, pp. xiii+258, 1977. (Rodale Press Inc., Berkhamstead), £4·95.

The word "consumer" is still a new one in relation to health services in this country; indeed it sounds odd when applied to patients except where medicines are concerned. In part this is because the National Health Service has so far done little to encourage critical awareness of its performance. Ministerial response to criticism is usually defensive and misleading. Community Health Councils were supposed to give consumers a chance to influence the local provision of health services; all too often they have been either ineffective or the vehicle of strident pressure groups, uninterested in the real problems of the community. In fact the private patient is often the best example of consumerism in medicine. This could be defined as taking an intelligent interest in proposed investigations or treatment—in their purpose, their risks and their costs. For obvious reasons this attitude is much more widespread in the United States, though recent publications by *Which* are among the first indications that British consumers are beginning to look critically at how the Health Service works and at how much trouble X-ray departments take to minimize irradiation of their patients.

It is the latter which is the theme of *X-rays – more harm than good?*—a long and thorough examination of the problems of radiation and the consumer in the USA. Most radiologists asked to write a book with such a title would be hard put to it to think of more than three or four chapter headings. The sub-heading 'how you can protect yourself against unnecessary radiation by understanding the uses and misuses of diagnostic X-rays" would help a little but might give the impression of an approach hostile to radiology. In fact Dr. Laws, a physicist, writes in a balanced and sensible way and is clearly concerned to see a reduction in practices which lead to pointless irradiation of patients. The scope of the book is best indicated by giving some of the main chapter headings—"X-ray—uses, benefits, costs and risks"; "relieving anxiety with X-rays"; "ruling out the worst again and again"; "patterns of overuse—routine examination"; "special problems of women"; "mal-practice, defensive medicine and X rays"; "the worship of technique"; "how X rays affect people"; "risks associated with X-ray diagnosis"; "how to minimize your exposure to X rays".

Clearly this is a book written for the American public and many of the practices referred to do not occur in this country or are seen in a less severe form. Few, if any clinicians here now have X-ray equipment and add to their charges by taking their "own" X-rays. Private health insurance does little to encourage extra examination on the basis that "you've paid for it, you might as well have it". We are, by and large, applying the "ten-day rule" to our patients. Sheer lack of money has restrained the wholesale installation of expensive new equipment which then has to be used to justify its purchase. Nevertheless we do have our share of clinicians who favour the blunderbuss approach to diagnosis; examinations are often repeated rather than sending for the films taken at other hospitals; some dentists X-ray teeth six-monthly; films are still taken without coning the diaphragms to the cassette; out-of-date equipment results in substandard and often useless radiographs; X rays are requested for medico-legal rather than clinical indications. Such practices are described and commented on in this book in some detail. In the chapter "how to minimize your exposure to X rays" the patient is given a long check list of points to query in relation to the way they are examined. It would be easy to deride this by pointing out that it could produce chaos in an X-ray department if every patient insisted on applying it: but in fact it should be applied by *someone* to every department and if radiologists and radiographers do not bother, presumably the patient will have to.

It is sobering that a book of this sort should have been written. I do not know the American scene sufficiently well to say whether Dr. Laws has been consistently accurate in her description of practices in the USA but there is enough here to make any radiologist or radiographer look carefully at his or her practice. In particular it comes across clearly that communication between radiographers and patients, radiologists and patients, and between radiologists and clinicians are essential to reduce unnecessary irradiation of patients and to diminish the anxiety which patients may feel about those examinations they must have. It is difficult to say who should read this book. It does not take long to read and one would like to think that every radiologist and radiographer has had a look at it. Perhaps the best answer would be to put this book on the reading list for the Part 1 F.R.C.R. so that from the outset the radiologist in training was made aware of the patient's point of view.

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Renal angiography problems in live kidney donors

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ABSTRACT

We compared renal angiographic and operative findings in 88 live kidney donors. Fifty patients had normal arteriograms and uneventful nephrectomies. Abnormal renal parenchymal or main artery lesions were found in eight donors (9%). These included four renal artery stenoses; the kidney distal to the lesion was used for transplanting. Thirty one patients (35%) had multiple renal arteries. Only 24 of these (77%) were diagnosed at pre-operative angiography, though on review angiogram accuracy could be raised to 94%. Except for one patient the accessory renal arteries missed at angiography were tiny twigs; the small renal infarcts caused by ligating them did not impair transplant survival. There was one serious misdiagnosis of multiple renal arteries, preventable on review of the abdominal aortogram. We consider pre-operative angiography an essential step for the live kidney donor. It is the most accurate way of ensuring that his remaining kidney will be structurally sound. Finding multiple renal arteries has a decisive impact on management. Abdominal aortography rather than routine selective arteriography is the safe and therefore preferable approach to these patients.

Pre-operative renal angiography of donors for kidney transplantation is standard practice (Penn *et al.*, 1970; Farrell *et al.*, 1973; Spanos *et al.*, 1974). Probably the most important reason for angiography is to ensure that the kidney to be left behind in the healthy donor is structurally sound. The conventional indication is to determine whether multiple arteries are present in the kidney to be transplanted. Multiple renal arteries are not a contraindication to transplantation, but if they are a unilateral finding with a normal kidney, it is generally preferable to choose the contralateral single-artery kidney. In his classical monograph Boijsen (1959) found multiple renal arteries in 24% of renal angiograms. He comments that this figure is lower than that found in autopsy material, "due to the fact that smaller calibre arteries to the upper pole were not always demonstrable in the roentgenogram". We have had the opportunity of confirming this observation in our live kidney donors and report a comparison between pre-operative and surgical findings in these healthy patients.

PATIENTS AND METHODS

We aimed to review all 94 live donor transplants carried out in this hospital. Documentation was incomplete in four and arteriography had not been carried out in a further two donors. The angiograms and case notes of the remaining 88 donors were available for study.

Angiography

The standard examination was the abdominal aortogram, carried out via a transfemoral catheter. Rapid serial films were taken following pressure injection of contrast medium in the aorta. If there was doubt about any renal abnormality or multiple vessels, a selective renal arteriogram was then performed. This was only done rarely.

RESULTS

Group I

Fifty patients had *normal* aortograms and operative findings, allowing for the occasional small renal cortical cyst undetected on angiography.

Group II

Eight patients had *abnormal renal parenchymal or main artery lesions* (Table I). Three donors had single *renal cysts* at angiography. In an additional patient four small cysts were discovered at operation. *Atheroma* at the origin of the right renal artery was seen at angiography in two donors. A further patient (also appearing in Group III) had a similar stenosis at the origin of one of her two right renal arteries.

TABLE I

GROUP II. EIGHT PATIENTS WITH RENAL PARENCHYMAL OR MAIN ARTERY LESIONS (INCLUDING ONE PATIENT WITH RENAL ARTERY STENOSIS AND MULTIPLE VESSELS ALSO APPEARING IN TABLE II)

No. of donors	Angiogram diagnosis	Comments
3	Single renal cyst	—
1	Normal	Four small cysts found at operation in kidney used for transplant
3	Atheromatous narrowing at right renal artery origin	Right kidney distal to stenosis used for transplant. One patient had a stenosis of one of her two right renal arteries
1	Fibro-muscular dysplasia	Lesions confirmed at operation and on histology—this kidney used for transplant

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The right kidney was used for transplanting in these three patients. We did not seek operative confirmation of these right-sided stenoses, hidden behind the inferior vena cava at surgery.

Fibromuscular dysplasia was found in the proximal arterial segment of one kidney used for transplanting, with good radiological, operative and histological correlation (Fig. 1).

Group III

Thirty-one donors had multiple renal arteries (including one from Group II) (Table II). Early branching of the single main renal artery in one patient effectively added a further double vessel problem to the surgical series (Fig. 2).

Twenty-four of all the multiple vessels (77%) were seen at pre-operative angiography. In nine patients with double left renal vessels the right rather than the left kidney was chosen for transplanting. However, in one of these nine, early branching of the single right renal artery behind the inferior vena cava resulted in ligation of a small upper pole vessel at right nephrectomy (Fig. 3).

Review of the seven patients with unexpected additional renal arteries discovered at surgery showed the accessory renal vessel arising from the aorta on five angiograms. With hindsight the pre-operative angiogram success rate could therefore be raised from 77% to 94%. The additional vessel was small except in one patient where the angiogram misdiagnosis of single renal artery was very serious. At operation in this patient a second left renal artery supplying the whole lower renal pole was found and could also be seen on review of the angiogram. Left nephrectomy was abandoned, and the right kidney removed through a second incision.

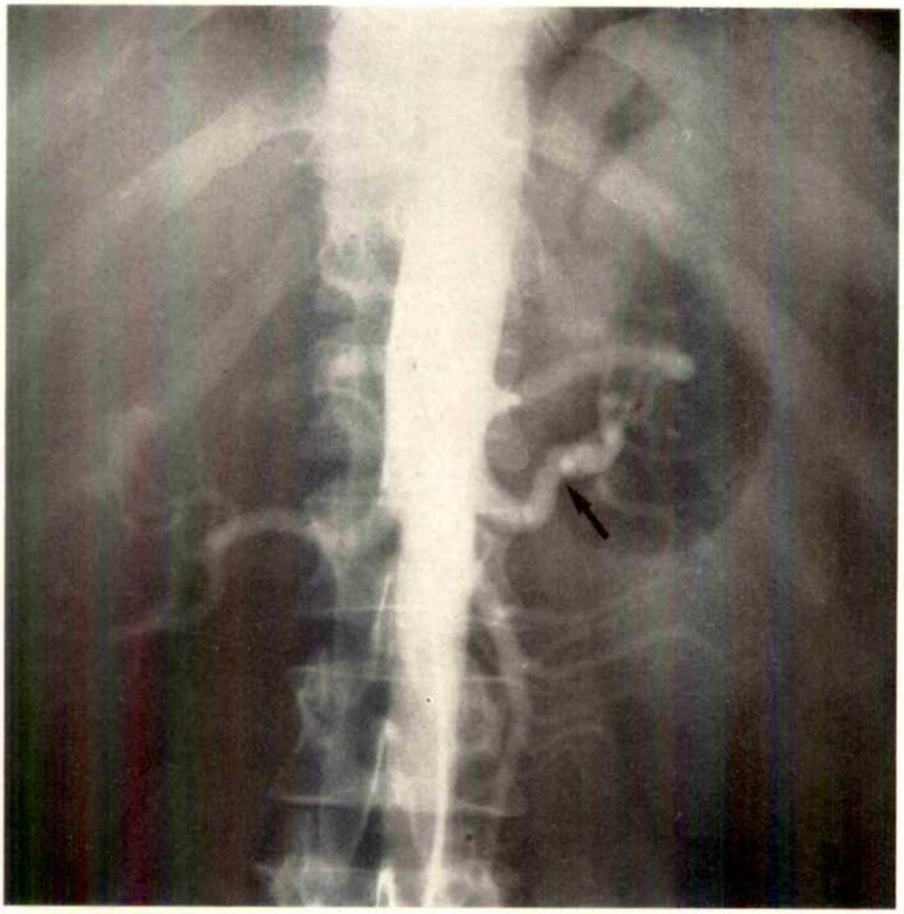

FIG. 1.

Left renal artery stenosis (arrow): this kidney was used for transplanting, excising the section of renal artery involved by fibrous dysplasia.

TABLE II

GROUP III. THIRTY-ONE PATIENTS WITH MULTIPLE RENAL ARTERY PROBLEMS AT OPERATION (INCLUDING ONE PATIENT ALSO APPEARING IN TABLE I)

	No. of donors	Initial angiogram diagnosis	Review angiogram diagnosis	Comments
Pre-operative and surgical agreement	11	Double right renal artery	do	Left nephrectomies
	9	Double left renal artery	do	Right nephrectomies. In one donor early branching of the right renal artery amounted to an accessory artery problem at surgery.
	3	Double right and left renal arteries	do	Two left nephrectomies with ligation of the small accessory vessel. One right nephrectomy with anastomosis of double vessels.
Pre-operative and surgical disagreeement	6	Single renal arteries	Five with accessory renal arteries	Accessory renal artery found first at operation. One left nephrectomy abandoned in favour of right.
	1	Multiple renal arteries: three on left, two on right	do	Third right renal vessel found and ligated at surgery.
	1	Single left, double right renal arteries	Very early branching of left main renal artery	Difficult left nephrectomy with undue blood loss.

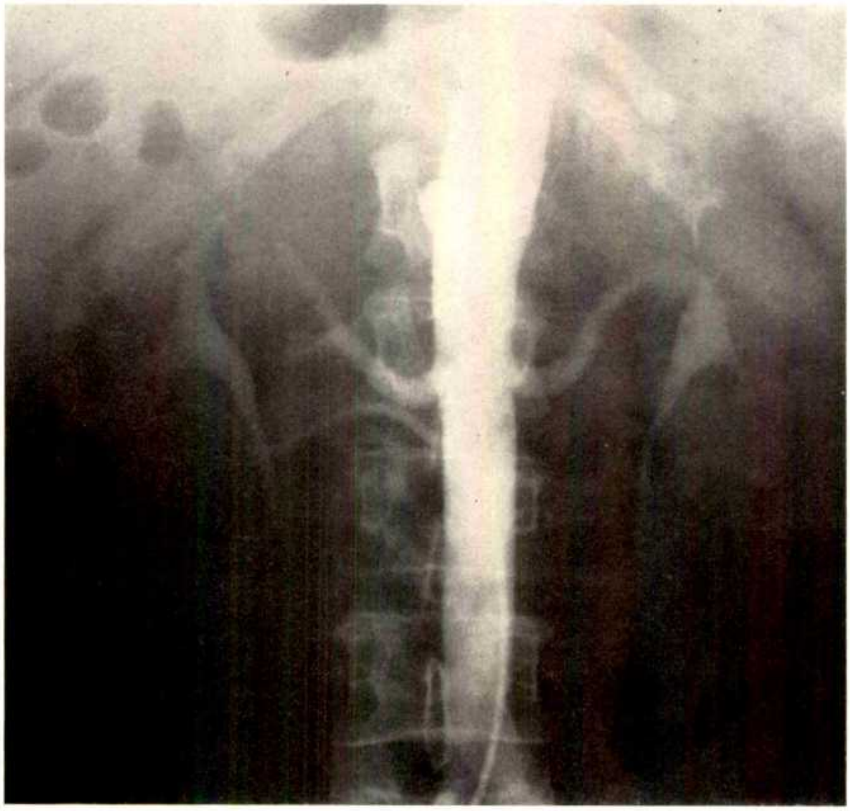

FIG. 2A.

Early aortogram frame: note that the renal arteries (two on the right, one on the left) are the first to fill from the aorta.

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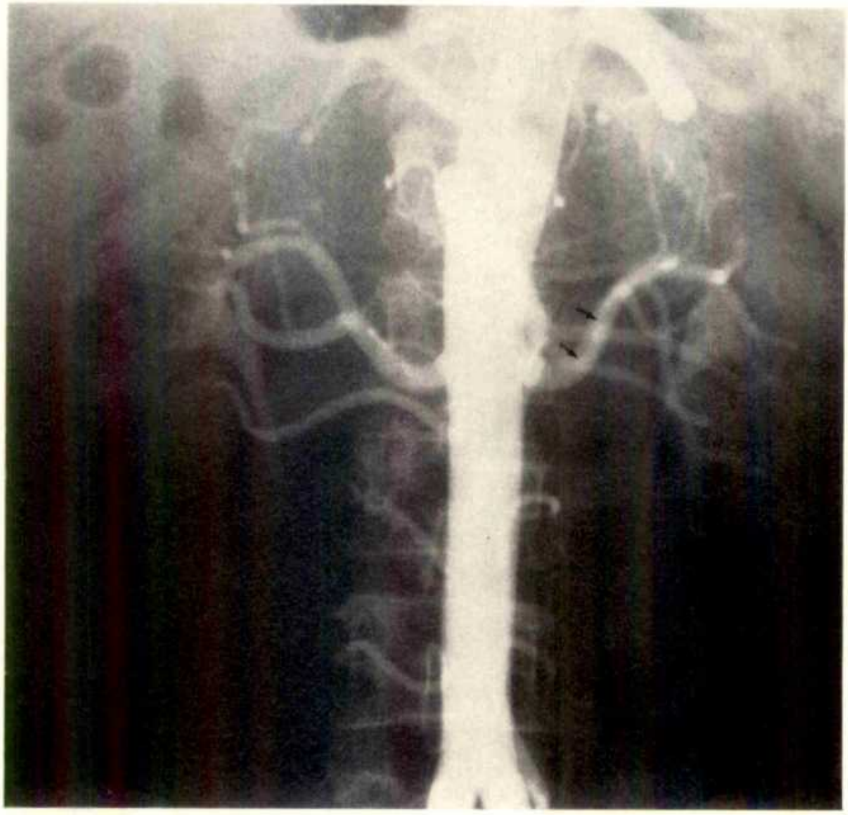

FIG. 2B.

A later frame shows a double contour of the distal left main renal artery (arrows). This is therefore a very early division of this artery, effectively making a double artery problem for the surgeon.

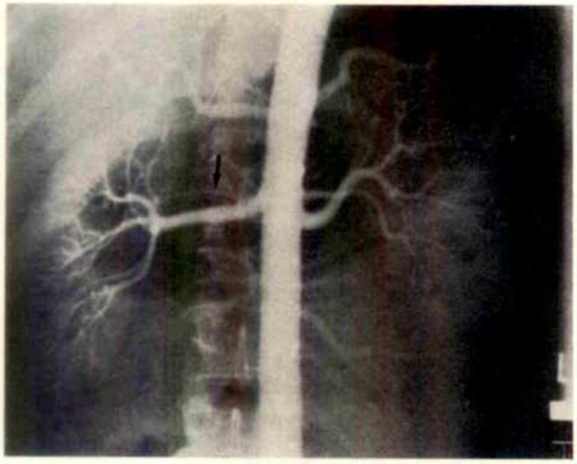

FIG. 3.

Aortogram showing two left renal arteries, but note that there is also an early branch arising from the single right main renal artery (arrow). This was effectively a double right renal artery problem for the surgeon.

In two donors the small accessory renal artery could not be detected even on the angiogram review. One of these showed three left and two right renal arteries on arteriography (Fig. 4), but an additional third right vessel was found at right nephrectomy. All of the small accessory arteries were ligated, with no problems in the recipient from the resulting small renal infarct.

Complications

One donor suffered a femoral artery thrombosis after the aortogram, requiring surgery. In another donor dissection of the renal artery occurred on selective catheterization of this vessel (Fig. 5). The complication was not recognized at the time, but clearly seen on review of the angiogram. Fortunately this was the kidney chosen for nephrectomy, when the pulseless renal artery had to be disobliterated before the kidney could be used for transplanting. The transplant later failed because of rejection.

DISCUSSION

We decided on this study in order to test the value and accuracy of pre-operative angiography in renal donors. Inevitably, we have shown that errors may occur, some of them potentially very serious. In this regard our experience is not dissimilar from that of previous reports (Farrell *et al.*, 1973; Spanos *et al.*, 1974). We remain convinced that angiography is an essential step in the pre-operative assessment of the prospective kidney donor. The most important reason is that the healthy donor must not be left with a kidney which is structurally compromised. It is a tragedy to deprive such individuals of a healthy kidney if the remaining one harbours chance findings like renal artery stenosis, a large cyst, or even a silent carcinoma. Arteriography is the most certain method of discovering such lesions.

For the proper management of the operative course, it is also essential to know about the arterial anatomy of the donor kidneys. It is possible to use kidneys with multiple arteries arising from the aorta, but such operations with additional vascular anastomoses impose extra risks on the success of the transplant. There is agreement that this risk is best avoided, if necessary by choosing the donor's right kidney despite its less favourable venous anatomy. This choice assumes pre-operative arteriographic knowledge of a healthy, multiple-artery left kidney. If a kidney with more than one artery does have to be used, it is best to know the details of the anomaly to be encountered. Such a kidney may be chosen because there are multiple renal arteries bilaterally.

The prevalence of abnormalities and anomalies in this series refers only to donors coming to nephrectomy. We have not reviewed all prospective donors who had angiograms: in such studies more problems may be expected, since unsuitable prospective donors will be eliminated on the angiographic findings. The four donors with renal cysts and four with main renal artery lesions amount to 9% of our patients. While renal cysts may be discovered by other means, angiography is the only way of defining renal artery obstruction before it leads to functional derangement. It was clear that our three patients with atheromatous narrowing of the right renal artery should

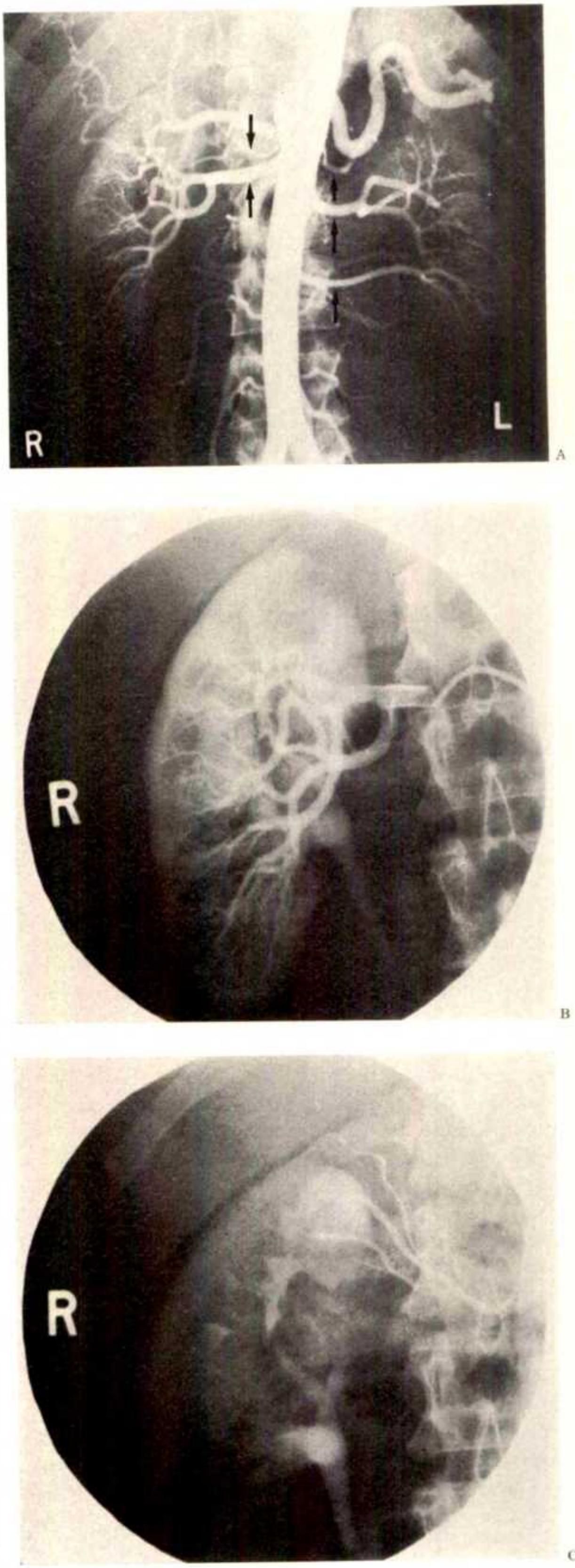

FIG. 4.

(A) This aortogram shows three left and two right renal arteries (arrows).

(B) Selective injection of large right main renal artery. Note vascular defect at upper renal pole.

(C) Selection injection of small upper pole right renal artery. Although two renal arteries appear to account for the whole of the vascular supply to this kidney, a third small upper pole vessel was found at operation.

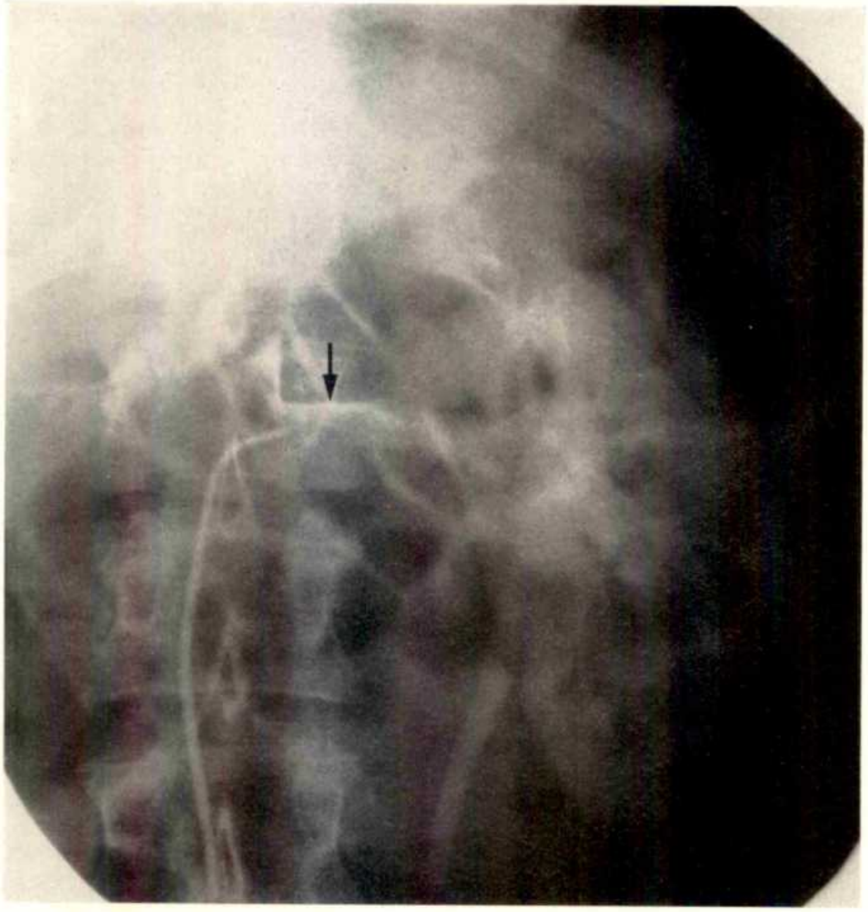

Fig. 5.

Selective left renal arteriogram: a pencil-sharp sliver of contrast medium remains behind on this late frame, within the vascular wall at the origin of the artery (arrow). This dissection was brought about by the selective catheter, and not recognized at the time. At operation fresh clot was found in the renal artery; this was removed, and the kidney used for transplanting.

donate their right, not left kidney. This risk of leaving a donor with an unhealthy kidney must be excluded, and needs no further emphasis.

Thirty-one of our 88 patients (35%) had multiple renal arteries, but only 24 of these (77%) were discovered pre-operatively. On post-operative review of the angiogram, the success rate could be lifted to 94%. Such second looks at angiograms known to harbour accessory vessels are instructive, but not a fair parallel to clinical practice. In two patients we were unable to find the additional renal vessel with hindsight, even on detailed selective arteriographic studies (Fig. 4). We suggest that an error rate of missing small additional renal artery twigs arising from the aorta is inbuilt to present day arteriography.

The renal infarcts produced by ligation of small accessory vessels have not been important in the follow-up of our transplants. However, one donor with a large second renal artery was missed. On review this was a clear though difficult anomaly on the abdominal aortogram. The misdiagnosis here was serious: the kidney was explored, and a second incision needed for obtaining the more favourable contralateral kidney.

It is not always appreciated that for the surgeon an early division of a single main renal artery makes for very similar difficulties as those encountered with double arteries. Radiologists must be sure that their reporting and communicating on this point is clinically relevant: the message "single main renal arteries" may be quite inadequate if it means an arterial trunk less than 1–2 cm long. Overlapping of the branches of such early divisions can be troublesome on A.P. projection (Fig. 2). Access to the origin of the right renal artery is more difficult than to the left, so that particular care is needed on this side with early division (Fig. 3).

Because of the obvious importance of multiple renal arteries in transplantation, selective arteriography of the donor's kidneys might be thought an essential part of the procedure. There is no doubt that it improves diagnostic accuracy. Against this must be weighed the increased hazard involved with the manoeuvre, illustrated by one of our patients who suffered a renal artery dissection. This event is a well recognized risk of selective arteriography (Talner *et al.*, 1975), though it was not spotted in our patient at the time. Tragedy for this donor was only averted because this kidney was the one chosen for nephrectomy on the grounds of being the left-sided organ.

We conclude that a meticulous abdominal aortogram should be the standard approach to renal donor angiography. Rapid early films are essential: the renal arteries with their large blood flow fill first, and this order of appearance can be very useful when there is doubt about the presence of multiple vessels (Fig. 2). Small accessory renal vessels may be missed in about 20% of patients, though with care this error rate could be driven down further toward the 10% level. The accessory arteries missed at this level are tiny, and ligating them is probably of no importance to the fate of the transplant. Selective renal arteriography as a routine manoeuvre might increase diagnostic accuracy yet further, but we do not think it is justifiable in the delicate setting of the healthy donor who may be harmed in this way. If the abdominal aortogram reveals a diagnostic problem, selective arteriography may well be indicated. We would like to suggest that this further procedure is only for experienced hands and eyes. Our misdiagnoses of major clinical importance have arisen because of inadequate interpretation of the abdominal aortogram, not because of failure to find tiny additional vessels at selective arteriography.

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The effect of osmotic diuresis on urinary iodine concentration using contrast media of differing osmolality

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ABSTRACT

The urinary iodine concentrations of a monomer (sodium iothalamate), a dimer (sodium iocarmate) and a non-ionic compound (metrizamide) have been compared in dogs with varying levels of solute excretion. All the animals were undergoing maximal antidiuresis.

In dogs with normal solute excretion, metrizamide and iocarmate produced higher urinary iodine concentrations than iothalamate. There was no significant difference between metrizamide and iocarmate. With increasing levels of solute excretion, the differences between the compounds were reduced.

These findings suggest that contrast media of reduced osmolality are unlikely to have a special place in advanced renal failure.

The excretion of urographic contrast media is accompanied by an osmotic diuresis. This is an important factor limiting the concentration of iodine in the urine (Benness, 1965; Cattell *et al.*, 1967; Saxton, 1969). Recently, contrast media have been developed which have a lower osmolality in solution than the compounds currently in use. Two such compounds are sodium iocarmate, a dimer of sodium iothalamate and metrizamide, a non-ionic compound. Table I compares the osmolality per mg iodine in solution of these compounds with that of the monomer, sodium iothalamate. When the amount of solute required to give an equivalent dose of iodine is considered, it can be seen that the osmotic diuretic effect should be less with iocarmate than iothalamate, and less with metrizamide than iocarmate. Animal studies have confirmed that the concentration of iodine in the urine after the injection of doses containing an equal amount of iodine is higher with iocarmate and metrizamide than with iothalamate (Hilal, 1970; Benness and Glazer, 1973; Golman and Almen, 1973; 1976) and higher with metrizamide than with iocarmate (Golman and Almen, 1976).

However, all these studies were carried out in animals which were concentrating their urine normally. In clinical practice urography with current contrast media is usually satisfactory in patients who are concentrating their urine. Difficulties occur when the kidneys are not concentrating well, especially when there is overt renal failure. In many such patients an endogenous osmotic diuresis contributes to the failure to concentrate urine. Since this is the type of patient who might benefit from the use of contrast media producing less osmotic diuresis, we decided to compare the excretion of sodium iocarmate and metrizamide with that of sodium iothalamate in animals with varying degrees of induced osmotic diuresis.

MATERIALS AND METHODS

Studies were carried out in mongrel dogs of either sex, weighing 13.5–22.5 kg, fasted overnight but without fluid restriction. All experiments were carried out under sodium pentobarbitone anaesthesia (Nembutal 20–30 mg/kg i.v.) with the dogs

TABLE I

OSMOLALITY COMPARISONS OF CONTRAST MEDIA

Contrast	Type of compound	Osmolality of solution (μosmol/mg I in solution)	Dose of contrast given	
			mg I/kg	solute/kg (μosmol)
1. Sodium iothalamate	Monomer	5.18	500	2590
2. Sodium iocarmate	Dimer	3.40	500	1700 (65%)*
3. Metrizamide	Non-ionic	1.62	500	810 (31%)*

*Figures in brackets indicate solute load as a percentage of the solute load given with the monomer.

breathing spontaneously through an endotracheal tube.

Through a suprapubic laparotomy, both ureters were catheterized at pelvic brim level with soft polythene tubing (Portex umbilical cannula FG6, internal diameter 1.4 mm). Blood samples were taken through a catheter in the inferior vena cava. Blood pressure was monitored via a catheter in the femoral artery connected to a Statham transducer.

In order to obtain comparable resting rates of urine flow, all animals were studied under conditions of maximal antidiuresis. This was achieved by giving 2 μg 1-deamino-8-D-arginine vasopressin (DDAVP) intravenously. After 45 minutes, urine was collected for the measurement of flow rate and osmolality. Dogs were divided into three groups, given mannitol as follows:

Group A. No mannitol.

Group B. Loading dose of 1.5 mOsm/kg of 5% mannitol followed by a constant infusion to achieve a steady moderate, osmotic diuresis (0.5–0.8 ml/min).

Group C. Loading dose of 3.0 mOsm/kg of 5% mannitol followed by a constant infusion to achieve a steady large osmotic diuresis (2.2–3.2 ml/min).

After 45 minutes stabilization on the above infusions, three 15-minute control urine collections were made. Each group was then divided into subgroups 1, 2 and 3 which were given sodium iothalamate, sodium iocarmate and metrizamide respectively. The dose for all three contrast media was 500 mg iodine/kg injected over 30 seconds. Further urine collections were obtained at 0–3, 3–10, 10–20, 20–30, 30–45 and 45–60 minutes after the injection of contrast. In the analysis of the results the 0–3 minute urine collection has been excluded as this is affected by the washout of the renal tubules, collecting systems and ureteric catheters (Morales *et al.*, 1950; Chinard, 1955). Heparinized blood samples were taken at the beginning and end of each urine collection.

The concentration of contrast medium in plasma and urine was measured by a spectrophotometric method similar to that described by Purkiss *et al.* (1968). The osmolality of plasma and urine was measured on an advanced osmometer. Statistical analysis of the results was by Student's *t* test.

RESULTS

Comparable basal rates of urine flow and solute excretion were obtained in 36 dogs. Twelve dogs were studied at each level of solute excretion. These groups of 12 dogs were divided into three subgroups of four dogs, and each subgroup received a different contrast medium (Table II).

Group A. DDAVP only (Table III)

In all urine collections the iodine concentrations with iocarmate and metrizamide were significantly higher than those with iothalamate ($p \leq 0.05$). There was no significant difference between the iodine concentrations with metrizamide and iocarmate at any time.

The mean urine flow rates with metrizamide were less than those with iocarmate, which were in turn less than those with iothalamate. However, a significant difference was only consistently seen between metrizamide and iothalamate.

Group B. DDAVP/moderate mannitol diuresis (Table IV)

The urinary iodine concentrations with iocarmate were significantly higher than those with iothalamate up to 20 minutes. The iodine concentrations with metrizamide were significantly higher than those

TABLE II

MEAN CONTROL URINE FLOW AND SOLUTE EXCRETION RATES

GROUPS (12 DOGS IN EACH)

Subgroups given different contrast media (four dogs in each)	A. DDAVP*		B. DDAVP/moderate mannitol diuresis*		C. DDAVP/large mannitol diuresis*	
	Urine flow rate (ml/min)	Solute excretion (μosm/min)	Urine flow rate (ml/min)	Solute excretion (μosm/min)	Urine flow rate (ml/min)	Solute excretion (μosm/min)
1. Sodium iothalamate	0.14	351	0.72	657	2.63	1520
2. Sodium iocarmate	0.16	327	0.74	761	2.84	1604
3. Metrizamide	0.16	340	0.70	755	2.52	1636

*There is no significant difference ($p \leq 0.05$) in urine flow rate or solute excretion between subgroups 1, 2 and 3 within Groups A, B and C.

TABLE III

Group A. DDAVP only

(a) Mean urine contrast concentration (mg I/ml)

Collection period (min.)	3–10	10–20	20–30	30–45	45–60
1. Iothalamate	63	79	91	105	111
2. Iocarmate	128	136	147	145	139
3. Metrizamide	155	145	159	160	146
1.v.2.	0.001	0.001	0.01	0.01	0.02
1.v.3. $p \leqslant$	0.01	0.01	0.001	0.001	0.05
2.v.3.	NS	NS	NS	NS	NS

(b) Mean urine flow rate (ml/min)

Collection period (min.)	3–10	10–20	20–30	30–45	45–60
1. Iothalamate	2.28	1.26	0.73	0.46	0.34
2. Iocarmate	1.58	0.92	0.58	0.37	0.29
3. Metrizamide	1.37	0.73	0.46	0.32	0.26
1.v.2.	NS	0.05	NS	NS	NS
1.v.3. $p \leqslant$	NS	0.02	0.01	0.05	NS
2.v.3.	NS	NS	NS	NS	NS

TABLE IV

Group B. DDAVP/moderate mannitol diuresis

(a) Mean urine contrast concentration (mg I/ml)

Collection Period (min.)	3–10	10–20	20–30	30–45	45–60
1. Iothalamate	66	58	49	44	37
2. Iocarmate	96	75	58	51	42
3. Metrizamide	123	82	65	53	45
1.v.2.	0·01	0·05	NS	NS	NS
1.v.3. $p \leqslant$	0·01	0·01	0·01	NS	NS
2.v.3.	NS	NS	NS	NS	NS

(b) Mean urine flow rate (ml/min)

Collection period (min.)	3–10	10–20	20–30	30–45	45–60
1. Iothalamate	2.85	1.93	1.50	1.16	0.98
2. Iocarmate	2.41	1.62	1.32	1.09	0.93
3. Metrizamide	1.87	1.41	1.15	0.96	0.82
1.v.2.	0.01	0.01	NS	NS	NS
1.v.3. $p \leqslant$	0.001	0.01	NS	0.02	NS
2.v.3.	0.02	NS	NS	NS	NS

TABLE V

Group C. DDAVP/large mannitol diuresis

Mean urine contrast concentration (mg I/ml)

Collection period (min.)	3–10	10–20	20–30	30–45	45–60
1. Iothalamate	44	29	24	19	14
2. Iocarmate	44	29	23	18	15
3. Metrizamide	53	34	25	19	15
1.v.2.	NS	NS	NS	NS	NS
1.v.3. $p \leqslant$	NS	NS	NS	NS	NS
2.v.3.	0.05	0.02	NS	NS	NS

with iothalamate up to 30 minutes. There was no significant difference between the iodine concentrations with metrizamide and iocarmate in any collection.

The urine flow rates with iocarmate and metrizamide were significantly less than those with iothalamate up to 20 minutes. In addition, up to ten minutes the urine flow rate with metrizamide was significantly less than that with iocarmate.

Group C. DDAVP/large mannitol diuresis (Table V)

There was no significant difference in urinary iodine concentration with iocarmate and iothalamate or with metrizamide and iothalamate. There was a significant difference up to 20 minutes between metrizamide and iocarmate, but the actual differences were small.

There was no significant difference in urine flow rates between any of the compounds.

Discussion

Our results in dogs with no mannitol infusion confirm reports that in dehydrated animals the dimer iocarmate produces higher urinary iodine concentrations than the monomer iothalamate (Hilal, 1970; Benness, 1970; Benness and Glazer, 1973; Golman and Almen, 1976). They also confirm the findings of Golman and Almen (1973; 1976) in rabbits that the non-ionic compound metrizamide produces higher urinary iodine concentrations and less increase in urine flow rate than iothalamate. The findings differ from those of Evill and Benness (1974) who found no difference in dogs between metrizamide and iothalamate. However, they were using a smaller dose of contrast medium (125 mg I/kg) which would produce a smaller diuresis. Thus, Golman and Almen (1973; 1976) have shown that the differences between contrast media of different osmolality are less with lower doses.

We did not show any significant difference in urinary iodine concentration between iocarmate and metrizamide although it had been anticipated that the different solute load given with the compounds (Table I) would be reflected in the final urine. Our finding differs from that of Golman and Almen (1976) who obtained higher concentrations with metrizamide than iocarmate in rabbits.

This discrepancy raises an important point. To explain it we must consider what is happening not only in the proximal tubule but also in the distal tubule, where the level of antidiuretic hormone (ADH) activity modifies the degree of osmotic diuresis (Zak *et al.*, 1954; Orloff *et al.*, 1957). A non-reabsorbable solute produces an osmotic diuresis by reducing the amount of water reabsorbed in the proximal tubule. More of the filtered water is thus delivered to the distal tubule and so to the urine. The amount of water entering the distal tubule depends on the load of non-reabsorbed solute but the proportion reaching the urine also depends on the amount reabsorbed in the distal tubule under the influence of ADH. If the subject is dehydrated and reabsorbing water maximally the distal tubule may be able to reabsorb much of the additional water entering from the proximal tubule. Thus reabsorption of water distally may partially or completely obscure the effect of varying degrees of proximal osmotic diuresis. The level of ADH activity is therefore an important factor to be taken into account when comparing contrast media of different osmolality (Golman and Almen, 1976).

It seems likely therefore that the difference between our results and those of Golman and Almen (1976) can be accounted for by the differences in the two experimental models. Their rabbits were not fluid restricted and had preliminary urinary osmolalities of "over 600 mOsm/kg". In our dogs there was a much greater degree of initial antidiuresis—the mean preliminary urine osmolality being 2050 mOsm/kg. For the same reasons, the differences we observed between compounds of differing osmolality may be more evident in man in whom urinary concentrating capacity is less than in dogs. Thus the maximum urinary osmolality in man is approximately 1200 mOsm/kg (Pitts, 1974) and in patients coming to urography the urinary osmolality is considerably lower than this.

The studies with mannitol infusion were designed to simulate the endogenous solute diuresis of renal failure. In renal failure it is believed that the nephron population in the kidney is reduced and that the normal daily load of water and solute is all carried by the few remaining nephrons (Bricker, 1969). These nephrons are thus hyperperfused or subject to a constant endogenous solute diuresis. This contributes to the impaired urine concentrating ability of patients with renal failure.

In the dogs given a mannitol infusion sufficient to produce a moderate osmotic diuresis (Group B) solute excretion was increased to rather more than twice normal. This is equivalent to halving the nephron population so that each remaining nephron must carry double the solute load. In the dogs with a large osmotic diuresis (Group C) solute excretion was increased to about five times normal—equivalent to an 80% reduction of nephron population.

Under conditions of moderate osmotic diuresis (Group B) there were significant differences in urinary iodine concentrations between iocarmate and iothalamate and between metrizamide and iothalamate. These differences were proportionally less than in dogs with normal solute excretion. As in the dogs with normal solute excretion, differences in iodine concentration between iocarmate and metrizamide were not significant. When the baseline solute excretion was greatly increased (Group C) the differences between the compounds were almost completely lost.

These results show that any benefit obtained from using the compounds of reduced osmolality is decreased as the resting level of solute excretion increases. This must raise doubts about the value of dimers and non-ionic compounds in patients with renal failure in whom the endogenous osmotic diuresis is likely to be nearer that in Group C than in Group B.

In conclusion this study has confirmed the advantages to be expected from contrast media with reduced osmotic properties under conditions of normal solute excretion. It has also highlighted the importance of considering resting solute excretion and the degree of ADH activity when comparing the effects of contrast media of differing osmolality. The results indicate that contrast media of reduced osmolality are only likely to be of value in patients with impaired renal function when endogenous solute excretion is not excessive.

ACKNOWLEDGMENTS

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Book review

Radiographic Contrast Agents. Edited by Roscoe E. Miller and Jovitas Skucas, pp. xv+515, illus., 1977 (Baltimore-London-Tokyo, University Park Press), £21·25.

The two editors have written the opening six chapters—everything about barium sulphate. This first third of their book is superb, and I would like to quote extensively from their summary:

"All so-called 'colloidal' barium sulfate preparations for radiology contain additives or contaminants in small amounts that, through surface action, affect surface tension, hydration, particle charge, and pH. These physical properties markedly influence particle size, flocculation, suspension, and viscosity. These latter properties, in turn, largely determine the suspension's ability to settle, flow, bubble, form blood clots, and make lesion-like artifacts; to coat and stick to the mucosa, form various film thicknesses, crack, and achieve and maintain various degrees of density; and to be recorded on the radiograph.

"Most barium sulfate additives are not listed on the container, are almost invariably present, and form a coat that is adsorbed on the aggregate particles' surface. This covering may consist of many substances in a variety of patterns with multiple degrees of ionic charge and hydration.

"The radiologist, knowingly or unknowingly, purposefully or haphazardly, changes the viscosity, density, surface tension, and film-forming qualities of his suspensions by selecting different brands of barium sulfate and by choosing the concentration and mixing methods in their preparation . . .

"By understanding the basic physical, chemical, and colloidal properties of barium sulfate suspensions and by taking advantage of additives already present, the clinical radiologist can control the performance of his barium sulfate suspensions through intelligent modification. He can do this quite easily by altering rationally his preparation methods and by judicious combination of different compatible barium sulfate compounds in various proportions. With their multiple additives, the radiologist can then use these combined compounds under local conditions in different concentrations for numerous types and methods of examination with superior results . . .

"These seemingly simple, but fundamental procedures, let alone the theory behind them, have not been suggested previously in the radiological, medical, patent, or advertising literature."

This work goes a long way toward correcting our ignorance about the worst labelled substance in clinical medicine. The rest of the book contains expert contributions by 17 authors on hepatobiliary, pancreatic, genitourinary, angiographic, bronchographic, myelographic and miscellaneous contrast agents. There is a final section on paediatrics. These chapters are all clearly presented, and I thought the biliary section particularly good. Inevitably authors often have to go over ground already covered in other publications; the editors have set their contributors an unfairly hard task in matching the knowledgeable enthusiasm and originality of the opening barium chapters. The book is worth buying for these alone, and also as a compact practical reference work on all contrast media.

THOMAS SHERWOOD.

1978, *British Journal of Radiology*, *51*, 111–115

Ioglycamide (Biligram) studies in man—relation between plasma concentration and biliary excretion*

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ABSTRACT

Plasma ioglycamide concentration was linearly related to the rate of intravenous infusion over a dose range of from 1 to 4 mg per kg per min. The relation between plasma and biliary concentration of ioglycamide was studied in 15 anicteric patients with a T-tube *in situ*. Peak biliary concentrations and excretory rates of ioglycamide were seen when the plasma concentration was greater than 1500 μg per ml. The mean biliary transport maximum (Tm) for ioglycamide in man was 31.6 mg/min (range 22.0–40.4). The results suggest that near optimal concentrations of iodine in the bile duct can be obtained during intravenous cholangiography if ioglycamide is infused for one hour at a rate of about 4 mg per kg per min.

Methylglucamine iodipamide (Biligrafin—Schering Chemicals Ltd.) has been in use as a biliary contrast agent since 1953 and is still the only intravenous cholangiographic substance approved for use in the United States (Burgener and Fischer, 1975). A new cholangiographic agent, methylglucamine ioglycamide (Biligram—Schering Chemicals Ltd.) was introduced in 1964 (Hoppe, 1964) and is now used extensively, both on the Continent and in the United Kingdom. In a recent postal questionnaire survey conducted in Great Britain (Bell *et al.*, 1975) it was found that over 75% of radiologists were using ioglycamide in preference to iodipamide. When the standard 100 ml bottle of 17% ioglycamide (Biligram infusion—Schering Chemicals Ltd.) was used it was found that the time taken to administer the contrast material via the drip varied from 20 minutes to several hours. This vast range of rates of administration presumably reflects the controversy which exists in the literature regarding the relative efficacy of the different methods for performing intravenous cholangiography using either iodipamide (Feldman and Keohane, 1966; Darnborough and Geffin, 1966; McNulty, 1968; Payne, 1968; Foy, 1968; Margolin and Obata, 1968; Allen, 1969; Scholz *et al.*, 1975) or ioglycamide (Parkin and Herlinger, 1974; Cantwell, 1974). In view of the known hazards associated with intravenous cholangiography (Ansell, 1970) we decided to determine, in man, the lowest infusion rate of ioglycamide necessary to achieve optimal radiographic opacification of the bile duct. In order to determine this it was necessary to investigate (1) the relation between infusion rate and resulting plasma concentration of ioglycamide, and (2) the relation between plasma level and biliary excretion of the compound. This paper reports our findings.

MATERIALS AND METHODS

Relation between infusion rate and plasma concentration of ioglycamide

We studied 36 patients who had been referred to the Radiology Department for intravenous cholangiograms. All patients had a serum bilirubin of less than 25 mmol/l (< 1.5 mg/100 ml) at the time of study. A blood sample was taken before and at regular intervals during the infusion of ioglycamide using the opposite arm to that employed for the intravenous cholangiogram drip. The plasma ioglycamide concentrations were measured on the same day as the cholangiogram using the spectrophotometric method of Fleck *et al.* (1974). The contrast agent was infused intravenously using the commercially available 100 ml infusion bottles of 17% ioglycamide (Biligram—Schering Chemicals Ltd.). The rate of administration of the ioglycamide was controlled using an IVAC 531 infusion pump (IVAC Corporation, Harrow, Middlesex). The biliary contrast agent was infused at a rate of either 1, 2, 3 or 4 mg per kg body weight per minute for 60 minutes. The numbers of patients in each of the four infusion groups were as follows:

1 mg/kg/minute—5 patients
2 mg/kg/minute—11 patients
3 mg/kg minute—10 patients
4 mg/kg/minute—10 patients

The patients given 4 mg/kg/min of ioglycamide for 60 minutes had the infusion continued for a further 30 minutes at the slower rate of 1 mg/kg/min.

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*This work had received the approval of the St. Bartholomew's Hospital Ethical Committee and the informed consent of the patients was obtained before the investigations were performed.

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Relation between plasma and biliary concentration of ioglycamide in patients with a T-tube in situ

A total of 15 patients with a biliary T-tube *in situ* were studied. All patients had undergone cholecystectomy and exploration of the common bile duct for gall-stones. A post-operative T-tube cholangiogram was performed on the seventh or eighth post-operative day before clamping off the T-tube. The studies were all carried out two or three days later when the enterohepatic circulation of bile salts had become re-established. The serum bilirubin of all the patients was normal at the time of study. At the beginning of the experiment the T-tube was unclamped and the bile allowed to drain by gravity drainage. Two baseline ten-minute bile samples were taken before the intravenous infusion of ioglycamide was started. Bile samples were then collected at ten-minute intervals for the next 120 minutes.

Two patients were given a two-hour infusion of ioglycamide at a rate of 1 mg/kg/min. Seven patients received ioglycamide at a rate of 2 mg/kg/min; infusion times of either one hour (two patients) or two hours (five patients) were employed. Five patients had a one hour infusion at 4 mg/kg/min, followed by 30 minutes infusion at 1 mg/kg/min, while finally one patient received 6 mg/kg/min for one hour followed by 30 minutes infusion at 1 mg/kg/min. Blood samples were taken from all 15 patients before the ioglycamide infusion was started. Three or four further blood specimens were taken from each subject at intervals between 60 and 120 minutes after the beginning of the infusion. The plasma concentrations of ioglycamide were measured on the same day by the method of Fleck *et al.* (1974). The bile samples were stored at −20°C and later ioglycamide concentrations were measured spectrophotometrically using the method of Bell *et al.* (1978). The biliary secretion rate of ioglycamide in mg/min over any given period was calculated by multiplying the concentration of the contrast agent in the bile specimen by the volume of the ten-minute sample and dividing by ten.

Results

Relation between infusion rate and plasma concentration of ioglycamide

When the infusion rate of ioglycamide was increased from 1 to 4 mg/kg/min the plasma concentration appeared to rise in a roughly linear fashion. The levels reached at the end of the 60 minutes infusion were 286 (±45); 863 (±59); 1134 (±35); and 1484 (±106) μg/ml respectively in the 1, 2, 3 and 4 mg/kg/min infusion groups (see Fig. 1). Figure 2 shows the serial plasma concentrations of the ten patients given ioglycamide at a rate of 4 mg/kg/min for 60 minutes followed by 1 mg/kg/min

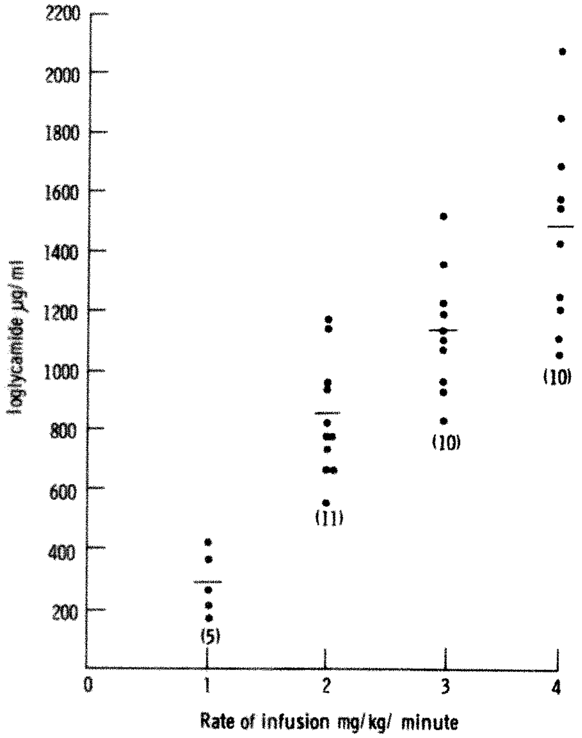

Fig. 1.

The concentration of ioglycamide reached in the plasma of patients at the end of a one-hour infusion cholangiogram at a number of different infusion rates.

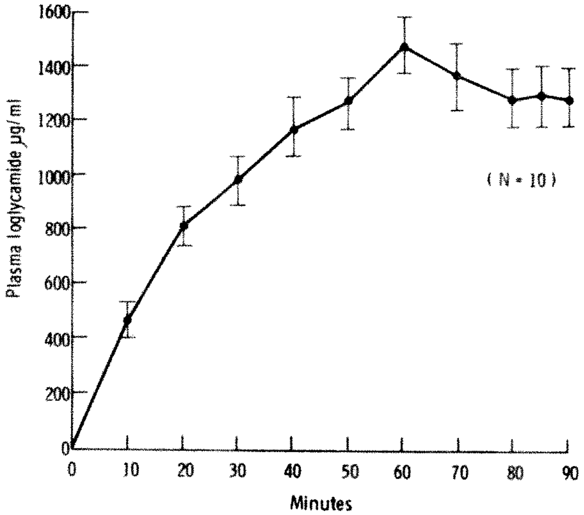

Fig. 2.

The plasma concentration of ioglycamide (mean ±SEM) in ten patients given 4 mg/kg/min for 60 minutes followed by 1 mg/kg/min for a further 30 minutes.

for a further 30 minutes. It can be seen that the plasma concentration of the contrast material reached by 60 minutes was maintained by prolonging the infusion at the lower rate.

Relation between plasma and biliary concentration of ioglycamide in patients with a T-tube in situ

The relation between plasma and biliary concentration of ioglycamide is shown in Fig. 3 while that for plasma concentration and biliary excretion of the compound is shown in Fig. 4.

As the plasma concentration of ioglycamide increased its biliary concentration and excretion rate also increased. Both the concentration and the biliary excretion of ioglycamide increased markedly at lower plasma levels but began to plateau off when the plasma concentration reached between 1250 and 1500 μg/ml. When the plasma concentration was in excess of 1500 μg/ml there was little further appreciable enhancement of biliary excretion of ioglycamide.

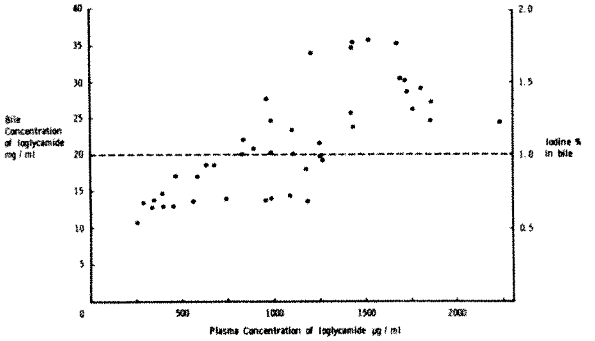

FIG. 3.

The relationship between plasma and biliary concentration of ioglycamide in man. The interrupted line represents a biliary concentration of 1% ioding.

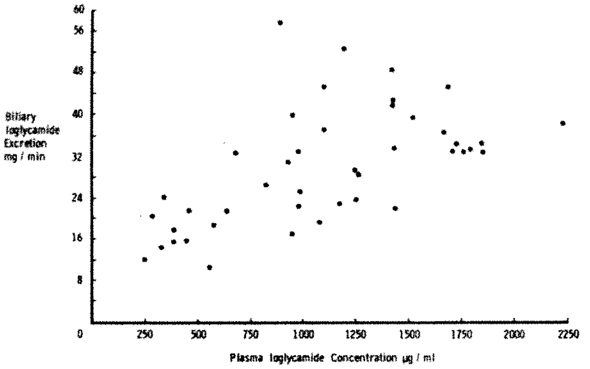

FIG. 4.

The relationship between plasma concentration and the rate of excretion of ioglycamide into bile in man.

Figure 5 shows the biliary excretion of ioglycamide in mg/min in the five patients given 4 mg/kg/min of ioglycamide for 60 minutes followed by 1 mg/kg/min for 30 minutes. The mean biliary excretion rate over the last 30 minutes of the infusion was 31.6 mg/min (range 22.0—40.4).

Relation of ioglycamide infusion rate to biliary concentration achieved

Table I and Fig. 6 show the concentration of the contrast agent appearing in the T-tube bile specimens from time 0 to 70 minutes after the start of

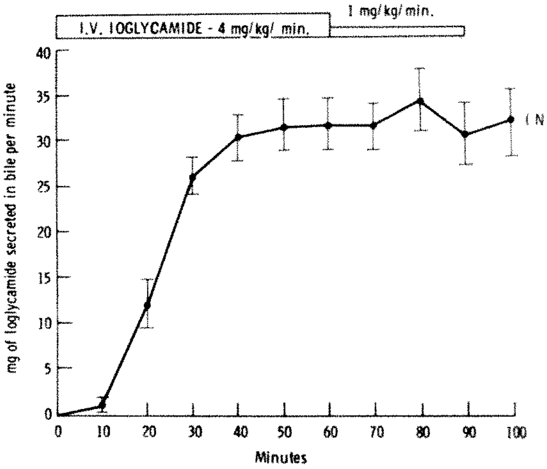

FIG. 5.

Biliary excretion of ioglycamide in mg/min in five patients given 4 mg/kg/min of contrast for 60 minutes followed by 1 mg/kg/min of contrast for a further 30 minutes. The biliary transport maximum for ioglycamide (Tm) is approximately 32 mg/min.

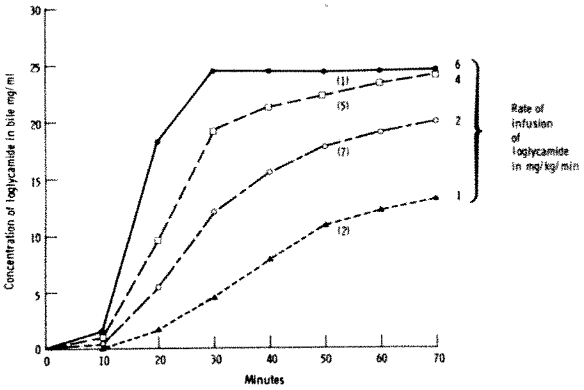

FIG. 6.

Mean concentration of ioglycamide achieved in the bile of patients receiving an intravenous infusion of the contrast agent at a rate of between 1 and 6 mg/kg/min. The number of patients studied in each group is shown in parentheses (see also Table I).

TABLE I

CONCENTRATION OF IOGLYCAMIDE (MG/ML) APPEARING IN HUMAN T-TUBE BILE—EFFECT OF RATE OF INTRAVENOUS INFUSION

	Time in minutes from start of i.v. infusion of ioglycamide						
Infusion rate	0–10	10–20	20–30	30–40	40–50	50–60	60–70
1 mg/kg/min. ($n=2$) mean range	0.0 (0–0.0)	1.6 (0.9–2.2)	4.5 (3.2–5.7)	7.7 (5.1–10.2)	10.9 (7.5–14.3)	12.1 (10.6–13.5)	13.2 (12.8–13.7)
2 mg/kg/min. ($n=7$) mean ± 1 SEM	0.3±0.2	5.4±1.4	11.9±4.8	15.5±1.7	17.7±2.0	19.0±1.9	20.0±1.9
4 mg/kg/min. ($n=5$) mean ± 1 SEM	0.7±0.3	9.4±2.1	19.1±1.6	21.3±2.2	22.4±2.8	23.3±3.1	24.1±3.1
6 mg/kg/min. ($n=1$)	1.5	18.3	24.5	24.5	24.2	24.5	24.5

the intravenous infusion of ioglycamide. Normally if a patient has a one-hour drip infusion cholangiogram the first radiographs would be taken approximately ten minutes after the drip was taken down. The concentration of ioglycamide (and hence iodine) achieved in the bile duct in the period between 60 to 70 minutes is thus of particular interest to the radiologist. There was a marked increase in the biliary concentration of ioglycamide in the 60- and 70-minute bile samples, when the infusion rate of the contrast agent was increased from 1 to 2 mg/kg/min. Again, when the infusion rate was increased from 2 to 4 mg/kg/min there was a further, though less pronounced, rise in biliary concentration. No further useful increase in biliary ioglycamide was obtained in the single patient in whom an infusion rate of 6 mg/kg/min was used instead of the 4 mg/kg/min régime. (see Fig. 6).

DISCUSSION

Our results show that the plasma concentration of ioglcamide was linearly related to the infusion rate over the dose range used. Using iodipamide in the dog, a similar relation between infusion rate and plasma level has recently been reported (Loeb *et al.*, 1975).

In the same paper Loeb *et al.* (1975) suggested that a hypobolic curve best described the relationship between plasma and biliary concentration of iodipamide. We did not feel justified in fitting our own data relating plasma and biliary ioglycamide levels to similar curves because of (a) the large scatter of results, and (b) the comparatively small number of observations at very low (*i.e.* 250 μg/ml) and very high (*i.e.* 2000 μg/ml) plasma ioglycamide concentrations. However, our results do show that at low plasma levels the biliary concentration of ioglycamide increases as the plasma level rises, but that once the plasma level reaches 1250–1500 μg/ml there is little if any increase in the concentration of bile.

If we conclude that plasma levels of ioglycamide of the order of 1250–1500 μg/ml are necessary to be quite sure that the patient is secreting the contrast agent into the bile at maximum possible concentration, we need to ask what infusion rate is necessary to achieve this? The results suggest that if ioglycamide is to be administered over a period of one hour the lowest rate of infusion which will achieve these levels consistently is 4 mg ioglycamide/kg/min.

In order to get good opacification of the gall-bladder as well as the bile duct it is an advantage to have the liver excreting the contrast medium at its highest possible concentration over a prolonged period of time. From Fig. 5 it can be seen that a constant high rate of excretion could be obtained by slowing the infusion rate from 4 mg to 1 mg/kg/min once the desired plasma concentration has been reached (see also Fig. 2).

Fuchs and Preisig (1975) attempted to measure the biliary Tm for ioglycamide in three patients with a T-tube *in situ* and obtained figures of between 19.8 and 23.7 mg/min. In their studies (Fuchs and Preisig, 1975) the ioglycamide was infused at a rate of only about 1 mg/kg/min. It is unlikely that sufficiently high plasma concentrations of the contrast agent were ever achieved to ensure optimal biliary excretion. In contrast, it can be seen from Fig. 2 and Fig. 4 that near optimal plasma levels of ioglycamide for biliary excretion were obtained by infusing at 4 mg/kg/min for one hour. We therefore think that the mean biliary excretion of ioglycamide recorded in these patients of 31.6 mg/min (see Fig. 5) is likely to be nearer the true Tm value than that found by Fuchs and Preisig (1975).

These results suggest that the optimum infusion rate for ioglycamide is 4 mg/kg/min for one hour. Ioglycamide contains 50% iodine so that this rate corresponds to a rate of iodine administration of 2 mg/kg/min giving a total dose of iodine in a 70 kg patient of 8.4 g iodine. This can be achieved in practice by infusing 100 ml of the commercially available 17% Biligram over 60 minutes. If there is a need to maintain an optimum plasma level the infusion may be continued at a reduced rate.

The clinical significance of the different infusion rates can only be determined by comparative clinical studies. An observation by Edholm and Jacobson (1959) does, however, suggest that the higher concentrations obtained with the higher infusion rates are likely to be important. These workers reported that a concentration of at least 1% iodine in the bile is required for adequate visualization of the duct. This is equivalent to 20 mg/ml ioglycamide. It can be seen from Fig. 3 that when the plasma ioglycamide concentration in the present studies was below 800 μg/ml all resulting biliary concentrations were below this critical level. When plasma concentrations were above 1200 μg/ml the majority of the patients could achieve biliary ioglycamide concentrations well above 20 mg/ml. These high concentrations were only consistently observed with an infusion rate of 4 mg/kg/min.

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The contribution of echography in the diagnosis of proptosis

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ABSTRACT

Echography was used to examine the retro-bulbar space of 150 patients with proptosis. An NE Diasonograph was used with an 8 MHz probe using a water bath in the supine position. Lesions were classified ultrasonically as (1) tumour, (2) inflammatory oedema (including pseudo-tumour or other granulomas), (3) traumatic, (4) dysthyroid ophthalmopathy, (5) normal. Thirty-one patients were placed in the tumour group but three of these were subsequently found to have granulomas. In addition, one patient with a normal ultrasonic appearance, was found to have a meningioma en plaque at operation. There were no false positive results in the inflammatory group but again one patient with a normal ultrasonic appearance was eventually diagnosed as having an orbital inflammatory process. The ultrasonic findings in inflammatory disease are non-specific and three were found to be associated with or possibly caused by venous thrombosis or arteritis of the orbit. The changes have to be distinguished from thyroid ophthalmopathy but this disorder is generally bilateral which is unusual in inflammatory disease. Traumatic oedema and haemorrhage are distinguished by the obvious antecedent history. Because of the variability of the amount and position of the retro-bulbar fat in the posterior part of the orbit, it is necessary to make a comparative scan of the normal orbit in all patients with suspected retro-bulbar pathology.

Proptosis is the commonest presentation of patients requiring investigation of the orbit. Although the presence of proptosis is usually obvious, until recently its investigation has been difficult, cumbersome and even dangerous, using the standard radiological techniques. The situation has been transformed in a few centres by the use of the CAT scanner but more widely by the application of ultrasonic B-scanning techniques (Coleman, 1972; Bronson, 1974). Although echography has been used for many years to investigate the retro-bulbar area (Ossoinig, 1967) using A-scan equipment, it is clear that many workers (Gitter *et al.*, 1969) have had difficulty in interpreting this type of scan. The purpose of this paper is to review the B-scan ultrasonic features of 150 consecutive patients referred for investigation of the retro-bulbar space and to highlight some of the difficulties encountered in technique and interpretation.

PATIENTS AND METHODS

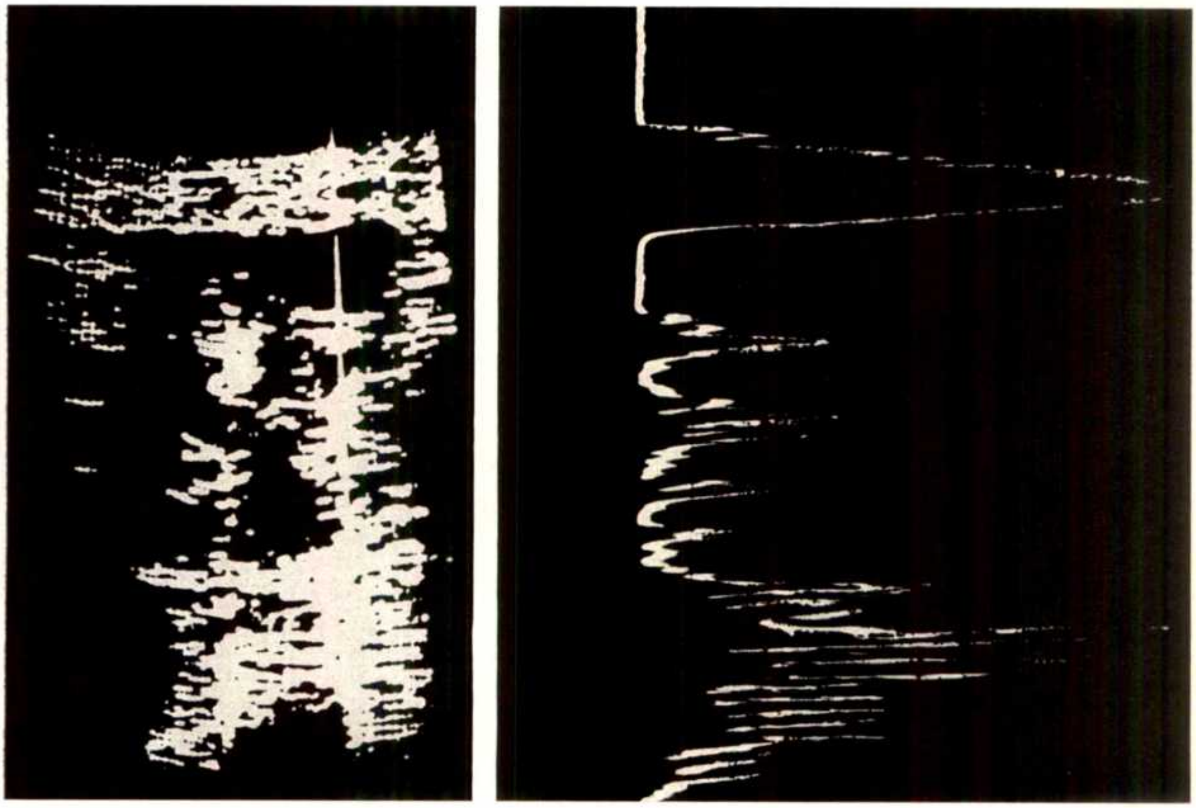
The 150 patients ranged in age from five to 85 years. All but four of the examinations were carried out by the same observer and an ultrasonic diagnosis was made in ignorance of the clinical diagnosis as far as this was possible. Biopsy or operative confirmation of the ultrasonic diagnosis was made in 37 of the patients. In the remainder, the clinical progress, the patient's response to treatment or in the case of those with dysthyroid ophthalmic disease, biochemical and immunological data were used to establish a clinical diagnosis. An 8 MHz focused transducer was used in an NE Diasonograph 4102. The technique of examination was similar to that described previously (Sutherland and Forrester, 1974). Approximately half the scans were made using a storage oscilloscope, the remainder with a simple open shutter grey scale technique. In the patients suspected of dysthyroid ophthalmopathy, extra-ocular muscle enlargement was graded on an arbitrary scale of 1 to 4. The results of a detailed study of these patients are being published elsewhere (Forrester and Sutherland, 1977).

RESULTS

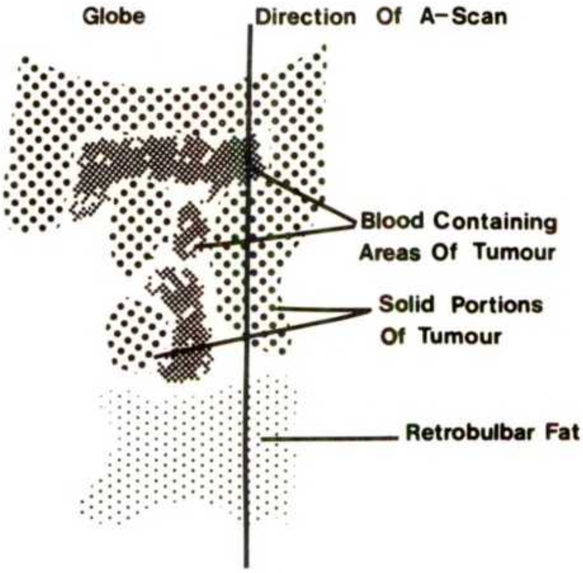
The patients were divided according to ultrasonic diagnosis under the following headings: (1) tumour, (2) inflammatory/oedema (with or without pseudo-tumour), (3) traumatic (including post-operative), (4) dysthyroid ophthalmopathy and (5) normal. These groupings were selected as they are diagnostic categories on which management decisions may be made.

1. *Tumour*

The ultrasonic diagnosis of "tumour" was made when a comparatively transonic filling defect was found in the retro-bulbar fat, in the absence of any abnormality of the optic nerve or extra ocular muscles. Thirty-one patients were placed in this category and 23 were confirmed by biopsy or operation. In six others the diagnosis had been previously established histologically and the orbital lesions represented local recurrence of tumour or the development of spread from an adjacent neoplasm. In two the diagnosis was not confirmed as the patients died elsewhere. In 28 of the cases the ultrasonic diagnosis was in agreement with the clinical or histological diagnosis. In three others a false positive diagnosis of tumour was made, histology subsequently showing the lesion to be a pseudo-tumour or localized inflammatory process. The histological types of tumour which were identified included lymphangioma,



A

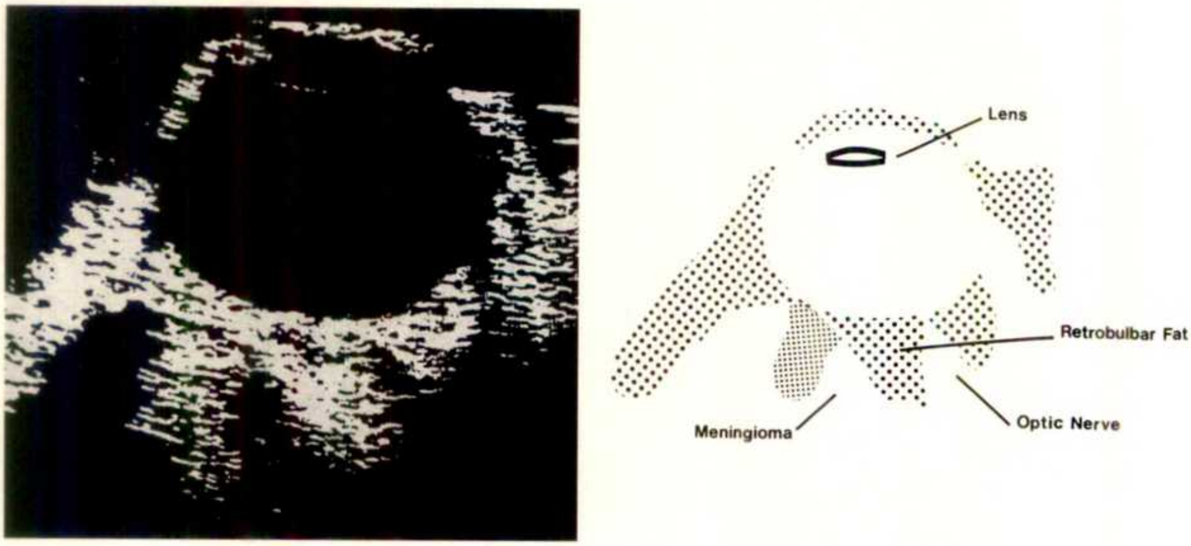


B

FIG. 1.

Haemangioma, (A) showing the typical heterogeneous appearance of the tumour, (B) the A-scan confirms the presence of echo free fluid filled spaces in the tumour.

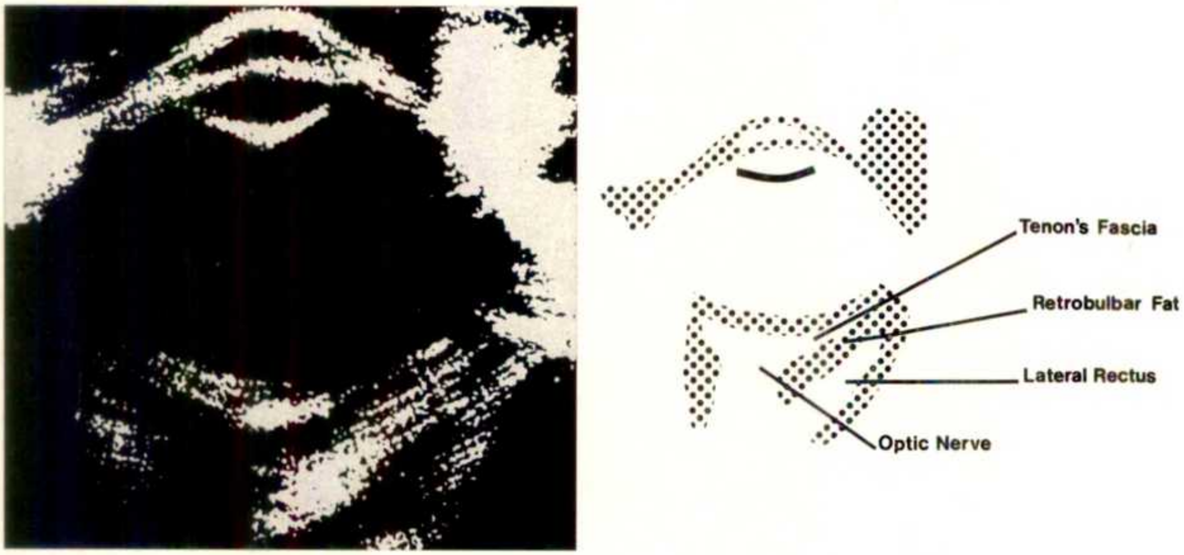
lymphosarcoma, haemangioma, carcinoma of the frontal sinus, naso-pharyngeal carcinoma, chordoma, meningioma, schawannoma and metastatic deposits from primary bronchial and breast carcinoma. The pathological nature of the tumours could not be decided with confidence from the ultrasonic appearances except in the case of haemangioma and lymphangioma when the characteristic vascular and lymphatic spaces were readily identified as echo free areas (Fig. 1). The remaining neoplasms produced non-specific echo patterns of lower average amplitude than the surrounding fat echoes and this feature allowed them to be seen as filling defects in the fat (Fig. 2).



A B

FIG. 2.

Meningioma of lateral orbital wall displacing the retrobulbar fat and optic nerve medially.



A B

FIG. 3.

Acute inflammatory change with obvious oedematous thickening of lateral rectus, the optic nerve, and fascial planes of the orbit.

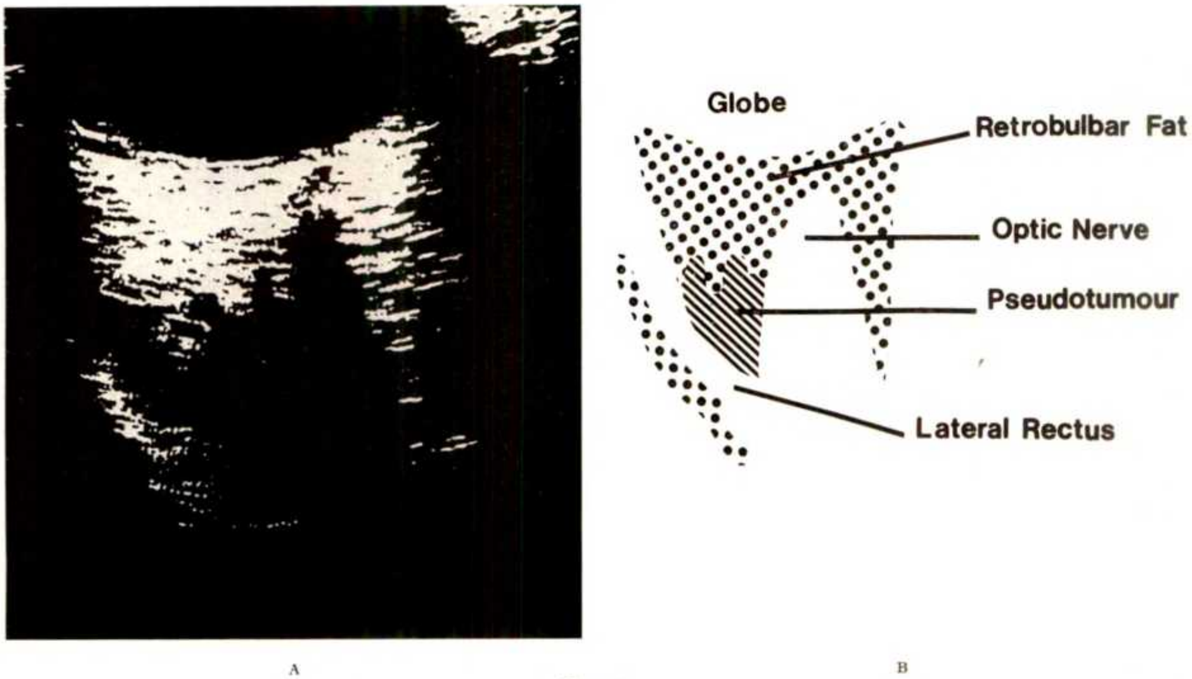


FIG. 4.

Pseudo tumour—an irregular localized filling defect is evident on the lateral aspect of the optic nerve posteriorly. The lateral rectus muscle is enlarged due to inflammatory involvement.

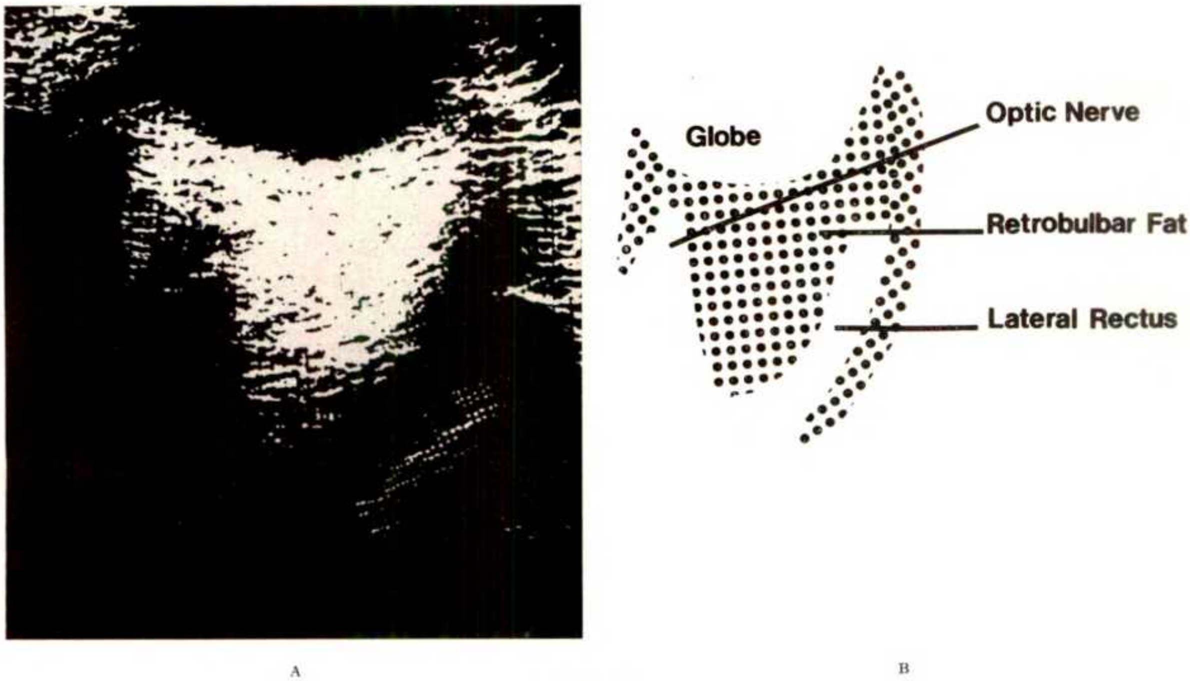


FIG. 5.

Severe dysthyroid ophthalmopathy with grade 3 enlargement of the lateral rectus muscle.

2. *Inflammatory/oedema*

There were 22 patients in this category and in six biopsies were carried out. The ultrasonic diagnosis was made on the basis of increased transonicity of the fat in the region of the optic nerve and of the lateral rectus or other extra ocular muscles. Occasionally in severe acute inflammatory conditions, evidence of a transonic division of the retro-bulbar fat in the position of Tenon's fascia was seen and presumed to be due to oedema or inflammatory exudate (Fig. 3). A pseudo-tumour or a granuloma was diagnosed when a mass-like filling defect accompanied these oedematous or exudative changes (Fig. 4). Nineteen of the 22 patients in this group were considered to have an inflammatory basis for the appearances as judged by clinical progress or by biopsy. In the remaining three the oedematous changes were associated with a vascular abnormality of the orbit (carotid-cavernous fistula, orbital vein thrombosis and temporal arteritis). Ten were thought to have pseudo-tumour formation. Four of these were confirmed histologically and one was found to be a sarcoid granuloma. In one patient with inflammatory muscle changes a pseudo-tumour, diagnosed by biopsy, had not been identified ultrasonically.

3. *Traumatic*

Fourteen patients were placed in this group. Nine had had recent direct injury to the orbit, two with retained extra-ocular metallic foreign bodies. The remaining five were post-operative cases referred with suspected haematoma formation. Filling defects in the retro-bulbar fat suggesting localized collections of blood or fluid were found in one of the post-operative cases and in one of the patients with direct trauma. The remainder were found to have ultrasonic changes similar to those found in the inflammatory group and thought to be due to either oedema or haemorrhage.

4. *Dysthyroid ophthalmopathy*

Sixty patients with this condition were evaluated ultrasonically. Enlargement of the extra-ocular muscles (predominantly the inferior and lateral recti) was apparent in 28 patients with clinical evidence of exophthalmus and in 20 of 32 patients with no clinical evidence of dysthyroid ophthalmic disease. There was no correlation between the severity of muscle swelling and the degree of exophthalmus or other dysthyroid eye changes (Fig. 5).

5. *Normal*

Twenty-three patients with normal ultrasonic findings were found in a miscellaneous group of patients with slight proptosis. Clinical diagnoses included polyneuritis, orbital myositis, myasthenia gravis, third cranial nerve palsy and two patients with central retinal vein thrombosis. One false negative "normal" examination was encountered in a patient with a meningioma en plaque in the roof of the orbit which was demonstrated angiographically.

DISCUSSION

In the clinical managenemt of proptosis, assuming that thyroid disease has been excluded by clinical, biochemical or immunological tests, the principal problem is to discriminate between those patients requiring operation and those who can be managed conservatively, broadly those with tumours or foreign bodies and the rest with a heterogeneous group of inflammatory or oedematous disorders. In this comparatively small series of patients with the diagnosis of tumour, the incidence of three false positives and one false negative result seems satisfactory, is similar to the findings of Coleman (1972) and validates the method used to distinguish between tumour and pseudo-tumour, namely the identification of increased transonicity of the extra-ocular muscles. The distinction between cystic and solid tumours has been greatly assisted by the use of grey scale techniques which demonstrate the weaker echoes arising from a solid tumour more readily. Nevertheless an A-scan through the lesion can still be helpful and Ossoinig (1974) maintains that the arrangement of the echo amplitudes obtained in this way may be diagnostic of the histological type of the tumour. We have found this to be true only in haemangiomas or lymphangiomas. The absorption of ultrasound by a solid tumour may occasionally be useful in distinguishing it from a cystic structure because of the shadow that such a tumour causes and densely cellular meningiomas may produce this effect. Coleman (1972) suggests that the appearance of the margin of a tumour may be of value in identifying its type. With our equipment we have not been able to demonstrate this. As the identification of a tumour depends upon its displacement of the retro-bulbar fat it is possible to miss lesions at the apex of the orbit where the comparatively transonic muscle cone is formed around the equally transonic optic nerve. Similarly en plaque lesions adjacent to the orbital walls may not be recognized. Coleman (1972) stated that it was only necessary to examine the affected orbit but it has been our experience that there is sufficient variability between patients, particularly in the amount of fat in relation to the muscle cone to make it necessary to compare the abnormal orbit with the other side. We therefore routinely examine both orbits in all patients suspected of a retro-bulbar lesion. In general the ultrasonic appearances of inflammatory conditions of the orbit are non-specific and in three patients they were considered to be due to vascular disorders of the orbit. By contrast two patients with ocular vein thrombosis had normal retro-bulbar appearances. Only when a mass lesion accompanies the changes can one be fairly certain that it is a granulomatous inflammatory disorder. However, from the point of view of management, the demonstration of a muscle abnormality will be sufficient in almost all cases to distinguish between a benign and a malignant proptosis. In the absence of clinical or other evidence of thyroid disease, the differentiation of unilateral dysthyroid muscle abnormality from inflammatory muscle change is impossible. However, in our group of dysthyroid patients only six had unilateral proptosis and in three of them the ultrasonic changes were bilateral so that only a few patients come into the difficult category as bilateral inflammatory disease is extremely rare. This observation is another reason for examining both orbits in all patients with proptosis. In the investigation of traumatic cases, echography may be useful firstly in identifying localized haematomas which may be restricting muscle movement and which the ophthalmologist might wish to drain and secondly, in the localization of foreign bodies in the orbit. Even if these are radio-opaque the ultrasonic examination may give valuable information in determining their exact relationship to the globe as in such patients the vitreous is usually blood stained and funduscopic exclusion of an intra-ocular or intra-mural foreign body may not be possible. In 22 of the 23 "normal" patients the majority of whom have been followed for more than a year and the remainder for at least six months, no evidence of a retro-bulbar lesion has come to light. The remaining patient in the group was found to have a plaque-like meningioma of the orbital roof—a very difficult lesion in a very difficult site.

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Book reviews

Osteoarthritis of the Hip. (Pathogenesis and consequent therapy). By R. Bombelli, pp. x+136, illus., 1976 (Berlin, Springer Verlag), DM166.

Professor Bombelli makes a case for a more traditional approach to the surgery of the hip in this condition, particularly in young patients where a hip replacement may have many years exposure to the risks of loosening and late infection.

He has been impressed by the ability of bone to remodel in certain circumstances, and his surgical techniques have been designed to alter the direction of forces acting on the hip joint. In particular, extreme valgus osteotomy not only produces symptomatic improvement, but he believes that the resulting tension on the superior joint capsule induces an osteophytic shelf along the superior acetabular margin with consequent increase in the weight-bearing area. His theory is illustrated with a wealth of vector diagrams and applied mathematics as well as radiographs, but the book is really of interest only to people involved in hip surgery and, in particular, to the surgeon rather than the radiologist.

J. T. PATTON.

Ultrasonics in Clinical Diagnosis. Edited by P. N. T. Wells, pp. 195, illus., 1977 (Edinburgh, Churchill Livingstone), £5·50.

This is the second edition of a now widely accepted short textbook. It is in a soft cover and is essential reading for trainee radiologists and for radiographers training in ultrasound, although it should have a much wider appeal to undergraduates and clinicians. As before it has an introductory explanation of the basic physics and diagnostic methods used in clinical practice. The main part of the text describes and discusses the ever-increasing number of clinical applications of ultrasound. It is difficult for any textbook to keep pace with such rapid development but if there is any criticism it is that a disproportionate amount of space is allocated to ultrasonic investigations of the brain and relatively little to the newer and possibly more clinically useful developments such as intra-abdominal abscess detection.

The last chapter on biological effects is always reassuring.

A. B. AYERS.

1978, *British Journal of Radiology*, *51*, 122–126

Build-up and depth-dose characteristics of different fast neutron beams relevant for radiotherapy

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ABSTRACT

Build-up and central axis depth-dose curves have been obtained for d(50)+Be, p(42)+Be and d+T neutron beams. Measurements carried out with the collimator opening covered with a layer of lead showed that for all three neutron beams the entrance dose is approximately 60% of the dose at the maximum. Consequently the skin-sparing properties of these neutron beams will be approximately equal and comparable to those for electron beam therapy. Central axis depth-dose curves have been established for d(50)+Be neutrons at 129 cm SSD, for p(42)+Be neutrons at 125 cm SSD and d+T neutrons and ^{60}Co γ rays at 80 cm SSD. The 50% dose values in a water phantom are at depths of 12.7 cm, 12.0 cm, 9.7 cm and 12.7 cm respectively, for field sizes of approximately 15 cm × 20 cm. Insertion of a 6 cm thick nylon filter in the p(42)+Be beam increases this value from 12.0 cm to 13.5 cm. The gamma component for the d+T neutron beam is higher than for the cyclotron beams.

For radiotherapy purposes, the depth-dose distribution in tissue and the build-up of absorbed dose in the skin and subcutaneous tissue are two important physical characteristics. Central axis depth-dose curves are available for a number of different neutron beams (ICRU, 1977). However, comparison of measurements of different authors is complex, due to differences in field size, source-surface distance (SSD), phantom material and the quantity measured (total absorbed dose or neutron absorbed dose). The build-up of secondary charged-particle equilibrium is also dependent on the experimental conditions. For any one specific neutron beam, the curve representing the variation in ionization with increasing thickness of build-up material is dependent on field size, the presence of phantom material behind the ionization chamber, the use of air or tissue-equivalent (TE) gas flushing the chamber and the application of an absorber to remove charged particles from the beam (Zoetelief *et al.*, 1978). It was decided therefore to determine central axis depth-dose curves and charged particle build-up for different neutron beams with one set of detectors under similar experimental conditions.

The neutron sources studied were the reactions of deuterons on tritium (d+T) and 50 MeV deuterons on beryllium (d(50)+Be), which have both been in clinical use for some years, and the reaction of protons on beryllium (p+Be). This last reaction has been proposed as an alternative to the d+Be reaction, since the same particle energy can be obtained with a cyclotron of smaller size (Johnsen *et al.*, 1976). A linear accelerator employing the p(66)+Be reaction is already in preliminary use for treatment of patients (Cohen and Awschalom, 1976). Extensive information on physical characteristics of p+Be neutron beams, including microdosimetry and determinations of energy spectra, has recently become available (Amols *et al.*, 1978). However, these studies did not yield information concerning the γ-ray contribution and the effect of filtering the neutron beam.

EXPERIMENTAL TECHNIQUES

The d(50)+Be neutrons have been obtained from the isochronous cyclotron at Louvain-la-Neuve, Belgium, made by CSF. A multilayer collimator 105 cm thick, of steel, acrylic plastic (Perspex) and lead provided a 20 cm × 20 cm field at 129 cm distance from the target (Octave-Prignot *et al.*, 1976).

The p(42)+Be neutrons were produced by the synchrocyclotron at the Institute for Nuclear Physics Research, IKO, Amsterdam. Protons accelerated to 52 MeV were degraded in energy to 42 MeV by means of a 3.7 mm thick aluminium foil and fully stopped in a Be layer 11 mm thick.

A proton energy of 42 MeV was chosen as this energy seems to be well suited for a cyclotron therapy system. According to Jungerman *et al.* (1971) the neutron production cross sections for protons on a thin aluminium target are much lower than for protons of equal incident energy on a thin beryllium target, and in addition the resulting average neutron energy is lower for aluminium than for beryllium. Consequently the contribution of neutrons resulting from the aluminium foil will not have much influence on the build-up and depth-dose distributions. The beam was collimated by means of a tapered multilayer collimator consisting of 25 cm steel and 25 cm borated paraffin with a circular steel insert providing a field with a diameter of about 17 cm at 94 cm distance from the target; this is approximately equivalent to a square field of 15 cm × 15 cm. During some of the experiments, a 6 cm thick nylon filter (density, 1.15 g cm^{-3}) was inserted in the collimator opening near the target.

The d+T neutrons of the Amsterdam fast neutron therapy facility were produced with a sealed tube shielded by approximately 30 cm of steel and 19 cm of polythene followed by 3 cm of lead (Mijnheer *et al.*, 1978).

The measurements of build-up were performed with disc-type TE ionization chambers having a front wall of either 1.0 mg cm^{-2} aluminized Mylar or 0.2 mm TE plastic. The central axis depth-curves were obtained with the aid of a spherical TE ionization chamber and an energy-compensated micro Geiger-Müller counter surrounded by a ^{6}LiF cap 3 mm thick (Zoetelief *et al.*, 1978). All the ionization chambers were flushed with TE gas. The neutron and photon absorbed doses were derived from the responses of the TE chamber and GM counter by using a ratio of 1.05 for the $\overline{W}$ values of neutrons to photons in the TE gas, a ratio of 1 for the effective mass stopping powers of secondaries in wall and gas of the ionization chamber for both neutrons and photons, and a ratio of 1.045 for the kerma in TE plastic to that in soft tissue for d+T neutrons. For the higher energies of neutrons produced by the p+Be and d+Be reactions, a value of 1 has been taken for this kerma ratio due to lack of reliable data in this energy range.

The depth-dose measurements were carried out in a water-filled open top Perspex cube with outside dimensions of 30 cm and walls of 0.6 cm thickness.

The build-up measurements were carried out by adding discs of TE plastic against the thin front wall of the disc-shaped ionization chambers which were placed against a water or polythene phantom in order to obtain maximum backscattering, simulating the situation at the skin. The collimator opening or the ionization chamber were covered with a lead layer sufficiently thick to absorb charged particles originating from the collimator materials.

RESULTS AND DISCUSSION

Build-up of secondary charged-particle equilibrium

Figure 1 shows the curves of build-up of secondary charged-particle equilibrium for the three neutron beams. The results for the p(42)+Be beam are given for the situation with the nylon filter inserted in the collimator opening. As can be seen from this figure, the relative ionization at the entrance (which to a first approximation is proportional to the entrance dose) is approximately 60% of the maximum ionization for comparable field sizes for all three neutron beams. For the d+T neutrons, the maximum of the build-up curve is reached at a depth in unit density tissue of about 2.5 mm, whereas for the d(50)+Be beam the maximum is reached at a thickness of about 7 mm. The p(42)+Be neutrons have a broad maximum in the build-up curve between 10 and 15 mm, indicating that there are relatively more high-energy neutrons in this beam than in the d(50)+Be beam. The depths at which the maxima are reached are in good agreement with the maximum ranges of the recoil protons (ICRU, 1977).

The d+T build-up curve is not much different from the ones measured by Goodman *et al.* (1970) and Greene and Thomas (1968), but differs from the curve presented by Smathers *et al.* (1978). Recently, however, this group measured a much lower entrance dose of about 40% for a collimated d+T neutron beam (Otte *et al.*, 1977). It is probable that during their first measurements no attempt was made to remove recoil protons from the d+T neutron beam, as has been suggested for therapy conditions (Broerse *et al.*, 1972).

The build-up curve for the p(42)+Be beam without the nylon filter shows a steeper increase in ionization, whereas the maximum remains at about the same thickness. This indicates that the contribution of neutrons of lower energies is reduced by use of the nylon filter.

For the evaluation of skin damage, it must be realized that the critical layer of the epidermis is located at a depth between 15 and 100 μm for most

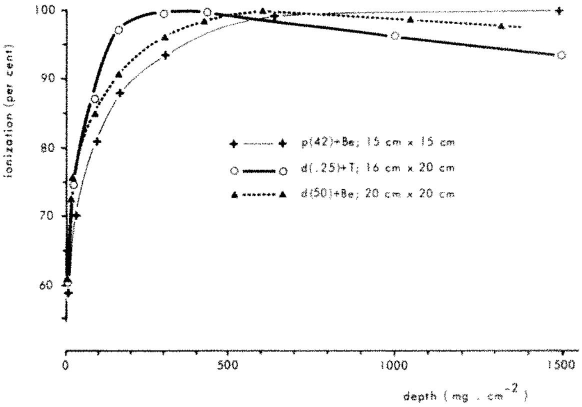

FIG. 1.

Charged particle build-up for d(0.25)+T, p(42)+Be and d(50)+Be neutron beams as a function of thickness of TE plastic.

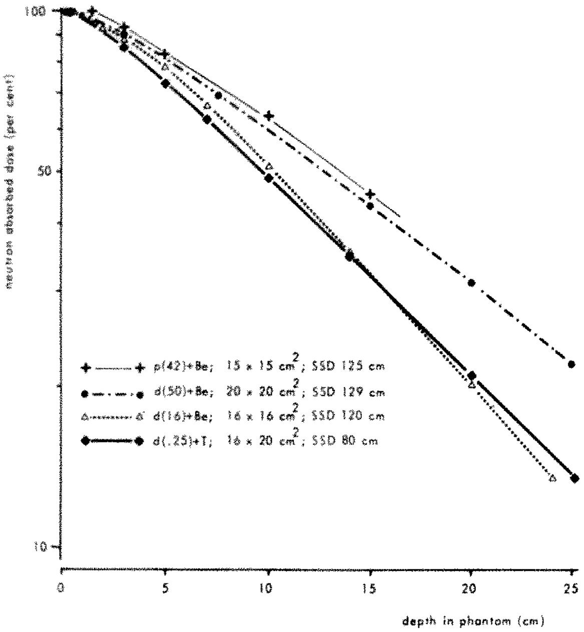

FIG. 2.

Central axis neutron depth-dose curves in water for d(16)+Be neutrons (Bewley and Parnell, 1969), d+T, p(42)+Be and d(50)+Be neutron beams of comparable large field sizes.

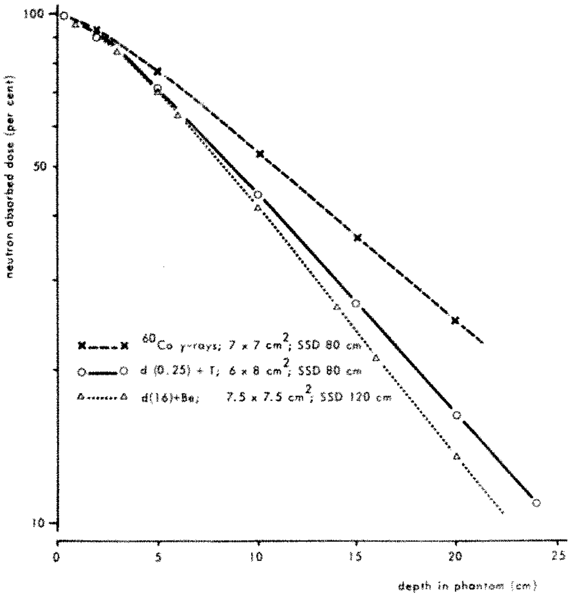

FIG. 3.

Central axis neutron depth-dose curves in water for d(16)+Be (Bewley and Parnell, 1969) and d+T neutron beams compared with the central axis depth-dose curve of ^{60}Co γ rays of comparable small field sizes.

parts of the body and that it is covered by a horny layer 15 μm thick (ICRP, 1975). Over this depth of 15–100 μm, the relative doses are nearly the same for these three neutron beams.

For the Hammersmith d(16)+Be neutron beam, Bewley (1971) measured a relative entrance dose of only about 20%. This lower value is probably due to the differences in experimental conditions. However, the dose at 100 μm is also not much lower than 60% for these neutrons, due to the steep initial rise of this curve.

If part of the field is covered with TE material during irradiation of patients, one should expect a more severe skin reaction at this position than in the rest of the field where the entrance dose will be lower. Clinical observations have shown, however, that there is no difference or only a very small difference in skin reactions between the covered and uncovered parts of the irradiated field (Battermann, 1977). Evidently the increase in dose due to the addition of TE material causes only a minor difference in biological effect. This might be attributed to the fact that the increase in dose is due to low LET particles, fast protons and electrons having an RBE not much different from 1. The α-particles, heavy recoils and low energy protons with ranges in tissue smaller or comparable to 100 μm have a much higher RBE (Broerse *et al.*, 1968; Bewley *et al.*, 1974). This contribution of high LET radiation with a relatively high RBE just below the surface will thus cause the skin-sparing with fast neutrons to be marginal and probably comparable to that in electron beam therapy, where the entrance dose amounts to 80–90% (ICRU, 1972).

Central axis depth-doses

In view of the differences in RBE, it is necessary to separate the contributions of neutrons and photons to the total absorbed dose. Central axis neutron depth-dose curves measured for d+T, p(42)+Be and d(50)+Be beams are given in Fig. 2. The data for p(42)+Be neutrons are for the situation with the nylon filter inserted and are converted from 94 cm SSD to a more likely therapeutic value of 125 cm SSD by means of a simple inverse square law correction. Such a conversion gave good agreement with experimental values for a collimated d+T beam (Mijnheer *et al.*, 1978). Also given are the data of Bewley and Parnell (1969) for d(16)+Be neutrons for a comparable field size.

As can be seen from this figure, the data for the d+T and d(16)+Be neutron beams at the given values of SSD are comparable. The depth dose curves for the filtered p(42)+Be and d(50)+Be

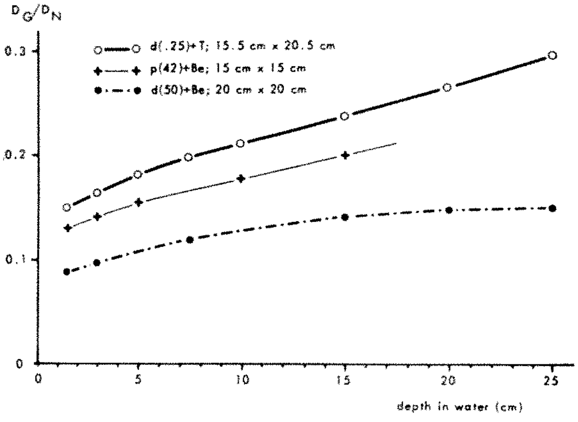

FIG. 4.

Gamma component of beams of d(50)+Be, p(42)+Be and d+T neutrons expressed as a percentage of the neutron absorbed dose, as a function of depth in the water phantom.

neutron beams show considerably better penetration characteristics. The 50% neutron depth-dose levels occur at depths in the water phantom of 12.7, 13.5, 10.2 and 9.7 cm respectively for the d(50)+Be, p(42)+Be (filtered), d(16)+Be and d+T beams at the given values of SSD for field sizes of approximately 15 cm × 20 cm. Increasing the SSD for d+T neutrons from 80 to 100 cm results in a 50% neutron depth-dose level at 10.2 cm for the same field size. The corresponding ^{60}Co γ-ray value is 12.7 cm at 80 cm SSD.

The depth-dose measurements with and without the nylon filter showed that the filter hardens the beam and increases the depth of the 50% neutron dose from 12.0 cm to 13.5 cm. A similar increase was observed by Johnsen *et al.* (1976) for a p(26)+Be beam. The rapid decrease in intensity within the first two centimetres observed by Smathers *et al.* (1978) for an unfiltered p(26)+Be beam could not be demonstrated for the p(42)+Be beam used for our experiments.

Depth-dose curves for a smaller field are given in Fig. 3, showing that here d+T neutrons have somewhat better penetration than d(16)+Be neutrons, although not as good as ^{60}Co γ-rays for the SSD generally used. Increasing the field size gives a greater improvement in depth dose for the d(16)+Be beam than for collimated d+T neutrons.

The ratio of the γ-ray absorbed dose to the neutron absorbed dose along the central axis of the field is given in Fig. 4 for the three measured neutron fields. The gamma component for the d+T beam is higher than for the cyclotron beams. As the p(42)+Be collimator was rather thin, improvement in the collimator design may reduce the ratio D_G/D_N for this beam.

CONCLUSION

The great similarity in build-up of ionization at depths between 15 and 100 μm of tissue measured with the same ionization chambers at three neutron beams suggests that the skin-sparing properties of these neutron beams should not be much different. Charged secondaries with relatively high LET and RBE increase below the surface much more rapidly than electrons and energetic protons of low LET and RBE. It can be concluded that the skin-sparing for fast neutron beam therapy will be comparable to that for electron beam therapy.

The central axis depth-dose curve will therefore determine the final choice of a neutron therapy machine, if other factors, *e.g.* output, reliability and price, are not considered. The neutron absorbed dose distribution at the SSD actually employed shows that the d+T beam is comparable to a d(16)+Be beam; d(50)+Be neutrons are superior in this respect. If sufficiently high dose rates can be achieved, the p+Be filtered neutron beam will provide the same advantages as the d+Be reaction for comparable energies of the bombarding particles.

ACKNOWLEDGMENTS

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Book review

Biological and Environmental Effects of Low-Level Radiation (1976). Proceedings of a Symposium, Chicago, November, 3–7, 1975 organized by the IAEA and WHO. Vol. I, pp. 364, $23.00; Vol. II, pp. 448, $28.00 (IAEA, Vienna).

A two-volume set of Symposium proceedings is more than twice as difficult to review than a single volume. A large proportion of the over 70 papers deals with effects caused by low LET radiation at single doses of 80 rad and above or at daily exposures of 2.5R or greater for substantial periods of time (or correspondingly damaging high LET exposures) and without consideration of how to extrapolate to "low levels". But some authors make a serious attempt to infer what the effects of low-level exposures might be. Naturally opinions will vary about the value of their proposals, especially when these were not based on an explicit statement of mechanism. In the more scientifically rigorous attempts the hypothesis was generally that the same effect can be caused by a single ionizing track or by an interaction of two tracks *e.g.* chromosome interchanges or double strand DNA breaks. Such a hypothesis means that the level of effect is a quadratic in dose, combining a linear term and a dose-squared term, and that only the linear term is of interest for low-level effects. Implications can be important: for instance hereditary damage in the offspring of experimentally irradiated mice will be largely attributable to chromosomal changes and experimental measurements of mutation rate in the gonads of irradiated mice will then over-estimate the induction rate of specific gene changes leading to reversible recessive mutations. If so, radiation-induced hereditary damage in man will be seen more in the first few generations and less in far distant generations than used to be envisaged. However, the possibility of repair of radiation-induced lesions in the hereditary material is an alternative explanation for many of the same observations and, if a biological process depends on the co-operation or interaction of two or more cells (? carcinogenesis), then the basic assumptions may not be applicable.

Very few observations were reported at environmental levels of exposure. Results collected over many years in an underground laboratory were claimed to demonstrate a real effect of ordinary terrestrial background, a stimulating effect on division of Paramoecium. Daily consumption of tritiated water giving a daily dose of 3 mrad to the developing rat fetus was said to slow down the development of righting reflexes during post-natal development. A dose-dependent increase in chromosome aberrations in cultivated blood lymphocytes was found in human beings exposed to an elevated background (up to a little over 2 rad annually) because of residence or work in a radioactive spa. Hadrons, even at much higher than terrestrial levels, were found not to show any unexpectedly damaging properties in mammalian tissues which may reassure future workers in a space environment.

Those interested in almost any specific action of ionizing radiation (apart from radiotherapy), from stimulation of pollen tube elongation to carcinogenesis, may find something worth reading and considering in one or both of these volumes.

R. H. MOLE.

1978, *British Journal of Radiology*, *51*, 127–131 FEBRUARY 1978

Effects of negative pions and neutrons on the growth of *Vicia faba* bean roots*

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ABSTRACT

Vicia faba bean roots have been irradiated with neutrons of various energies and with negative π-mesons, and the effect on the ten-day growth of the roots has been determined. The neutron irradiations were made in beams of 400 and 600 MeV maximum energy, as well as with neutrons from a plutonium-beryllium source (mean energy 4.4 MeV) and from a 14 MeV neutron generator. The bean roots have also been irradiated at various points along the depth-dose curve of negative π-mesons, including the region where the pions annihilate on coming to rest.

The results show a maximum relative biological effectiveness (RBE) of 3.7 for 50% reduction in ten days growth for stopped negative pions and values up to 3.3 for high-energy neutrons, compared to 5.5 for 14 MeV neutrons. The biological effectiveness of high-energy neutrons and stopped pions shows a more pronounced dependence on dose than does the effect with lower-energy neutrons.

Radiobiological research at CERN is primarily concerned with the study of the biological effects of high-energy particle interactions. This research has been limited to low dose-rate effects because of the low intensity of the secondary particle beams available (high-energy neutrons and pions) from the CERN accelerators. The aim of the research has been to determine the biological effectiveness of the high-energy radiation in order to provide some check on radiation protection norms for high-energy particles, which are essentially based on extrapolation from effects observed with low-energy radiations. The growth inhibition of the primary roots of *Vicia faba* seedlings was chosen as a suitable biological test system on account of its high sensitivity and the possibility of giving extended exposures by irradiating the beans at low temperature (4°C). Another advantage of this system is the possibility of measuring oxygen enhancement ratio (OER) *in vivo*.

Radiobiological research using high-energy particles has been further stimulated by the advent of high-intensity cyclotrons and the possibility of using their pion beams for radiotherapy. Similarly, studies using high-energy neutrons contribute information that may be useful for the optimization of neutron energy for radiotherapeutic applications.

BEAMS AND DOSIMETRY

The proton, neutron, and pion beams from the CERN 600 MeV synchro-cyclotron (SC) that were available prior to 1972 and were used for these studies have been described elsewhere (Baarli *et al.*, 1971). The main facility now in use for radiobiological studies using the improved CERN SC is the high-energy neutron beam produced by 600 MeV protons incident on a beryllium target (Baarli *et al.*, 1977). These will be referred to as 600 MV neutrons. The beam used had a uniform intensity distribution over a diameter of 14 cm, and the dose-rate in the beam, measured as a function of depth in a polythene absorber, is shown in Fig. 1. The bean roots were irradiated at the minimum depth possible when in a water tank (2.5 mm) and at the depth of the maximum dose-rate (20cm). The dose to the beans was estimated using a 0.1 cm^3 tissue-equivalent ionization chamber positioned in the bean irradiation tank. The same dose corrections were applied as for the 400 MV neutron beam (Baarli and Sullivan, 1972). The dose to the beans at the front of the irradiation tank and therefore at a small depth in the absorber will primarily be due to the short-range products from nuclear interactions. As the depth increases, the dose due to fast protons produced in the absorber builds up. Calculations indicate that at a depth of 20 g/cm^2 fast protons account for more than 75% of the dose in a monoenergetic neutron beam (Alsmiller *et al.*, 1970).

The first series of negative pion studies were carried out using the beam from the CERN SC at an average momentum of 175 MeV/c with a spread of 2%. More recently, irradiations have been made in the biomedical facility of the cyclotron at SIN (Swiss Institute for Nuclear Research, Villigen). The pion beam in this facility enters the irradiation cave vertically and has been set up to have a circular form at the irradiation position (Baarli, *et al.*, 1976; Nordell *et al.*, 1977). The bean-root tips are held at a precisely determined depth beneath a variable water absorber, as shown in Fig. 2. Also shown is the transmission ionization chamber used to control the irradiations, and an additional small ionization chamber placed underneath the bean tray to ensure

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*An earlier version of this paper was presented at the meeting on Biological Effects of High LET Radiation, London, 21 January 1977, held at the British Institute of Radiology.

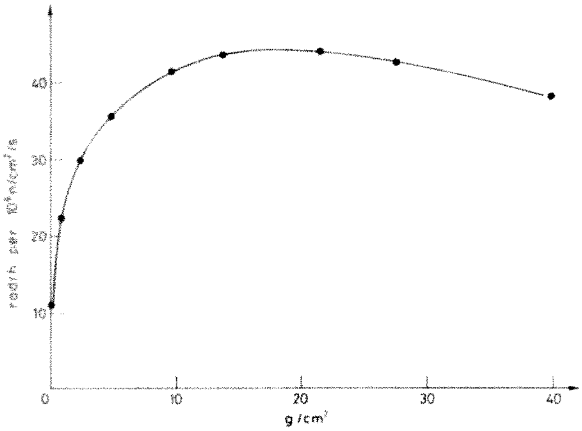

Fig. 1.

Dose in a 600 MV neutron beam as a function of depth in a polythene absorber.

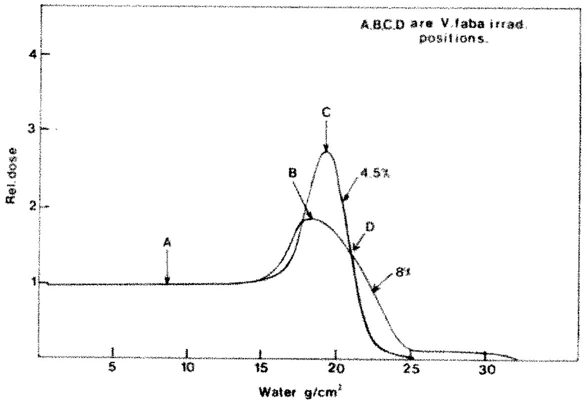

Fig. 3.

Depth-dose curves for pion beams of 4.5% and 8% momentum spread, showing the irradiation positions.

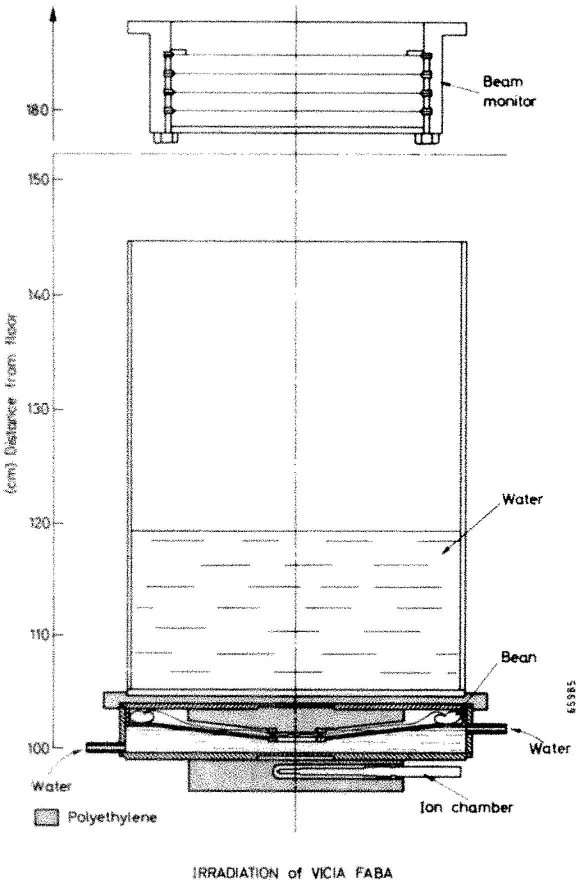

Fig. 2.

The arrangement for the irradiation of beans at a defined depth in a vertical negative pion beam.

that conditions remained constant during the irradiations. The dose-rate in the pion beam was measured using a parallel-plate tissue-equivalent ionization chamber with a diameter of 2 cm and spacing of 2 mm.

The relative dose as a function of depth of water absorber for the two pion beams used for irradiations at SIN is shown in Fig. 3. They had different momentum spreads, 4.5% and 8% of the initial momentum of 172 MeV/c. The actual peak dose-rate of the 8% beam was about twice that of the 4.5% beam. The doses that are measured are those to the tissue-equivalent ionization chamber, and no correction has been applied for possible differences between energy deposition in the chamber and in the beans due to differences in composition (Baarli and Sullivan, 1973).

As the pions slow down they interact with nuclei in the absorbing material, when a part of their rest mass is dissipated as kinetic energy of the nuclear fragments produced (nuclear stars). The proportion of the dose from these nuclear stars to the total dose varies along the beam and reaches a maximum at a point on the back edge of the stopped pion peak, where the maximum biological effectiveness may be expected.

Reference irradiations were made using ^{60}Co γ rays at dose-rates from 15 to 80 rad/h. Irradiations were also carried out with neutrons from a 14 MeV neutron generator (Laurent, 1974) and from a 50 Ci ^{238}Pu–Be source. The latter irradiations were made with the root tips positioned at 6 cm from the source where a dose-rate of about 4 rad/h was obtained.

BIOLOGICAL PROCEDURES

The Prolific Longpod variety of the broad bean *Vicia faba* was used for all neutron experiments, except the latest pion experiments where the Fillbasket variety was used. A comparison was made between the two varieties using ^{60}Co γ rays at low and high dose-rates, and no significant difference was found in the growth characteristics after irradiation (Bianchi and Hill, 1977). The method of growth followed closely that described by Hall (1961), where the beans are first soaked in water for three days, then planted in vermiculite, and after a further three days transferred to the growing-tank. The beans are selected for irradiation on the basis of the mean growth rate of their primary roots during the three following days and of their mean length. The selected beans were stored for a minimum of 24 h at 4°C before being irradiated at this temperature. After irradiation their length was measured and they were then returned to a growing-tank through which aerated water at 19°C was continuously circulated. The bean root length was measured daily for the ten days subsequent to the irradiation, and any lateral roots removed as they appeared.

RESULTS AND DISCUSSION

The observed reduction in the growth of the bean roots after ten days is shown as a function of dose for 400 MV neutrons in Fig. 4 and for pions in Fig. 5 together with the results obtained using ^{60}Co γ radiation. Straight lines have been fitted through the points by linear regression analysis over the range of 30% to 80% growth reduction. The results after irradiation in the stopped pion peaks of the beams with 4.5% and 8% momentum spread were found to fit the same line. A summary of the results obtained, expressed as relative biological effectiveness (RBE) for a 50% growth reduction of the bean roots after ten days, is given in Table I together with the dose-rates that were used.

The RBE of high-energy neutrons is found to be lower than that for conventional energy neutrons, as is expected from the calculations on which radiation protection norms have been based (ICRP, 1962). The values found for Pu–Be neutrons (average energy 4.4 MeV) and for 14 MeV neutrons agree well with those observed by Hall (1974). For the 400 MV neutron beam at 20 g/cm^2 depth, where the neutrons are in equilibrium with their secondaries,

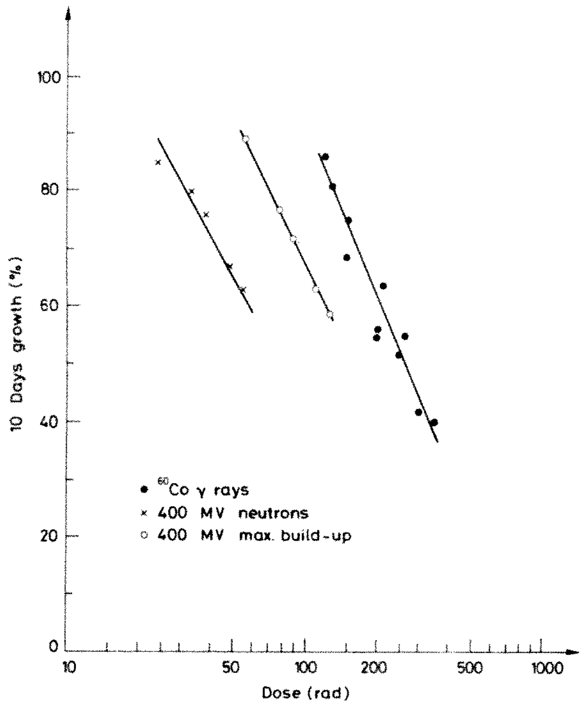

FIG. 4.

Dose-effect curves showing ten-day growth as a function of dose in the 400 MV neutron beam.

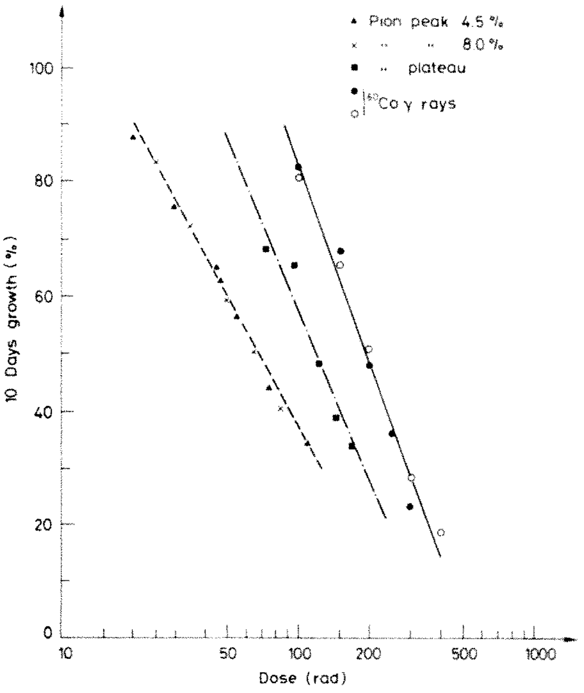

FIG. 5.

Dose-effect curve showing ten-day growth as a function of dose for negative pions.

TABLE I

Radiation used	RBE for 50% growth reduction	Dose-rate (rad/h)
600 MV neutrons (2.5 mm depth)	3.3	14
600 MV neutrons (200 mm depth)	1.7	46
400 MV neutrons (10 mm depth)	(3.3)	6
400 MV neutrons (200 mm depth)	(1.6)	12
14 MeV neutrons	5.4	≃8
Pu–Be neutrons	6.5	≃4
CERN π^- beams, front peak	(2.0)	3
back peak	(3.7)	3
SIN π^- beam, plateau	1.6	30
peak	2.8	≃40
back peak	3.5	75

( ) Lines extrapolated to 50% growth reduction.
600, 400 MV neutrons means neutrons generated by protons of 600 MeV, 400 MeV on a 5 cm thick Be target.

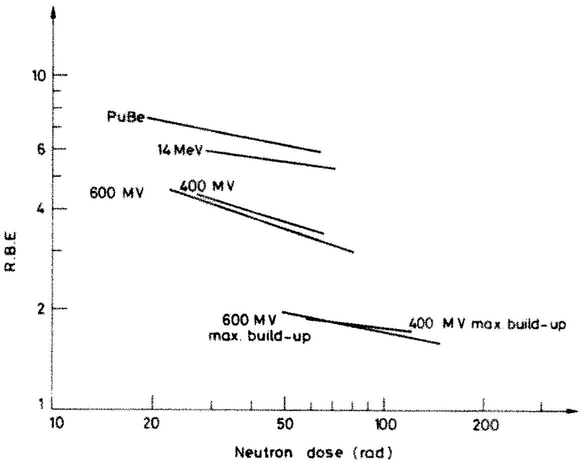

FIG. 6.
Variation of RBE with dose for neutrons.

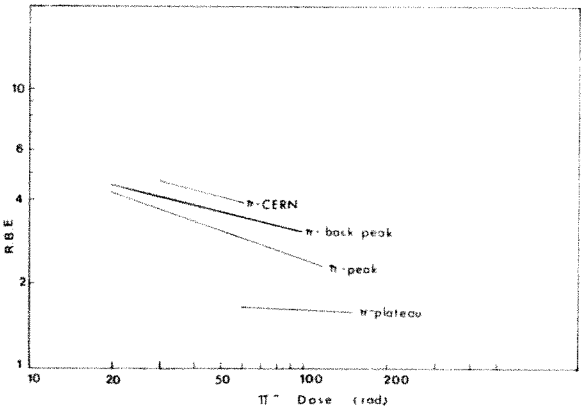

FIG. 7.
Variation of RBE with dose for pions.

the RBE is half the value obtained at small depths where the proportion of the dose due to short-range high-LET products from nuclear interactions is much higher. Both at small absorber depths and at maximum build-up, 600 MV neutrons appear to have a slightly lower RBE than the 400 MV neutrons, which is again consistent with predictions.

In the negative pion beam the dose from high-LET short-range interaction products is lowest in the plateau region where it accounts for only about 14% of the total dose, the rest being due to ionization by fast charged particles, whereas at the stopped pion peak this proportion is about 60% (Nordell *et al.*, 1977). The RBE values in the plateau and peak are consistent with a value of about four for the dose from the short-range nuclear star products. The high-energy neutron results are also consistent with this value for the RBE of the dose from the short-range secondaries. However, the physical data on the neutron and pion nuclear interactions and their biological significance are not sufficiently understood to enable a definite quantitative comparison to be made.

The proportion of dose from pion interactions is greatest on the back edge of the stopped pion dose-peak, and this proportion increases as the momentum spread of the pions decreases (Nordell *et al.*, 1977). This explains the highest RBE for stopped negative pions of 3.7 being found on the back edge of the CERN pion beam which had the narrowest momentum spread. An RBE of three has been reported for the stopped pion peak at Berkeley (Raju and Richman, 1972) and a similar value has been found for pion beams of different momentum spreads at Nimrod using the same biological end-point (Winston *et al.*, 1973).

The dose-effect curves shown in Figs. 4 and 5 are not parallel to the ^{60}Co control curve; this implies that the RBE will increase with decreasing dose. This rate of increase is similar for 400 MV and 600 MV neutrons and for the stopped negative pions, and is much more pronounced than for low-energy neutrons, as shown in Figs. 6 and 7. This increase in RBE with decreasing dose could have important implications for radioprotection where high-energy particles are present.

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The technical assistance of Mr. R. C. Raffnsøe in setting up and carrying out the measurements described here is greatly appreciated.

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Book review

Radiation and Cellular Control Processes, Edited by J. Kiefer, pp. xiv + 321, 1976 (Springer-Verlag, Berlin, Heidelberg, New York), DM.72.

This book records the proceedings of a conference held at the "Strahlenzentrum der Justus Liebig-Universitat", Giessen, Germany, from October 6 to October 10, 1975. The meeting was organized in co-operation with "Deutsche-Gesellschaft für Biophysik" co-sponsored by the commission of the European Communities. Forty delegates mainly from European Institutes gave 37 lectures, grouped in the book into three main chapters. The first chapter contains eight lectures on radiation and metabolic key processes, introduced by a review by J. M. Boyle (Manchester). A number of lectures are concerned with transcriptional organization of the ribosomal RNA genes (J. Retèl *et al.*), controls of DNA polymerase activity (H. Eckstein), DNA-specific labelling (M. Brendel), DNA synthesis (V. Wintersberger), general metabolism (J. Kiefer *et al.*) and the synthesis of inducible arginase after irradiation of yeast (E. Gocke *et al.*). A comparative study of sensitive and resistant strains of the slime mould, Dictyostelium, was discussed by P. E. Bryant.

The second chapter is concerned with problems of repair and recovery, mainly in yeast, E. coli and tetrahymena. A short review introducing repair in yeast (E. Moustacchi) is followed by 18 papers devoted to varying aspects of excision, post-replication and chromosomal repair. The final chapter consists of nine papers on cell division and progression after irradiation, in a variety of eukaryotic systems together with novel systems such as the moss Fumaria hygrometrica (v-Döhren) and lens epithelial cells (H. Pink and H.-R. Koch). Two papers, one by U. Wangenheim on Radiation and Endocellular Control of Cell Proliferation and a closing lecture by T. Alper on Modern Trends and Creeds in Radiobiology make interesting reading. There is a limited but adequate index to the whole volume.

The main value of the publication is centered on its specialization on systems other than mammalian and, to a lesser extent, bacterial cells. It forms a useful documentation of some of the ways this field has been developed, using the many advantages of yeast as an experimental cell system.

B. W. Fox.

1978, *British Journal of Radiology*, *51*, 132–138

The response of the mouse ear to heat applied alone or combined with X rays

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ABSTRACT

The effects of heat either alone or combined with X-irradiation were investigated in the skin of the mouse ear. Ears were heated for times ranging from 7.5 minutes to four hours in a water-bath at temperatures ranging from 39°C to 46°C. Severe heat treatment caused necrosis during the first few days after heating. Mild hyperthermia, which itself caused early transient reddening but no further visible changes, when given immediately after X rays enhanced the radiodermatitis which was observed during 10–50 days after treatment.

From a level of heating which is slightly less than that required to produce necrosis in any mice, an increase in temperature of 0.5°C caused an increase in the incidence of necrosis from 0 to 100%. For hyperthermia which enhanced radiodermatitis, an increase of 0.5°C was equivalent to an increase in X-ray dose of 10 to 15%.

For heat alone, the time required to produce necrosis in half the treated mice was reduced by one half for a rise in temperature of 1°C. For heat combined with X rays, the time required to produce a given enhancement of radiodermatitis was reduced by one third for a rise in temperature of 1°C.

Activation energies calculated using the Arrhenius equation were 580 kJ/mole for necrosis after heat alone and 1030 kJ/mole for thermal enhancement of radiodermatitis. These results suggest that different processes are involved in direct heat necrosis and thermal enhancement of radiodermatitis.

Mammalian cells may be damaged if they are maintained at temperatures greater than 37°C. Both the type and degree of injury depends on the severity of the heat treatment. Severe heat treatment causes tissue necrosis during the first few days after heating (Moritz and Henriques, 1947; Crile, 1963; Morris *et al.*, 1977) whereas moderate heating, which alone has little visible effect, may enhance the response to radiation (Robinson *et al.*, 1974; Field *et al.*, 1977; Stewart and Denekamp, 1977) or cytotoxic drugs (Hahn, 1975; Overgaard, 1976; Bleehen *et al.*, 1977). Recent experiments have suggested several reasons why malignant tissues might be more sensitive to heat than normal tissues (Suit and Schwayder, 1974; Leith *et al.*, 1977; Field *et al.*, 1977) and there are already several reports of cancer treatments using hyperthermia alone or in combination with X rays or drugs (Crile, 1962; Cavaliere *et al.*, 1967; Stehlin, 1969; Pettigrew *et al.*, 1974; Stehlin *et al.*, 1975; LeVeen *et al.*, 1976).

If hyperthermia is to be used rationally the therapist will require quantitative information about the response of both tumours and normal tissues which may be included in the treatment field. One of the factors which needs to be investigated is the relationship between heating time and temperature. Observations made on several different tissues suggest that for heat alone the time required to produce a given level of damage must be reduced by a factor of approximately two for a rise in temperature of 1°C (Moritz and Henriques, 1947; Crile, 1963; Morris *et al.*, 1977). This relationship, however, has been little studied for thermal enhancement of the radiation response. The aim of the present study, therefore, was to establish the relationship between heating time and temperature, both for the effect of heat alone and for thermal enhancement of radiation damage in one normal tissue. The mouse ear (pinna) was chosen, as this organ is easily heated by immersion in hot water and the reactions to the two treatment modalities may be scored without difficulty.

TECHNIQUES

Female CFLP mice were anaesthetized with pentobarbitone sodium (Sagatal) at 0.065 mg/g body weight for both hyperthermia treatment and irradiation. Heating was by immersion in hot water, using a thermostatically controlled water bath with a temperature variation of less than 0.05°C. Mercury thermometers, calibrated against a secondary standard, were used to measure the temperature of the water. It was assumed that the ear temperature was equal to that of the water since this was found to be the case for heating the tail of a rodent in a similar manner (Morris *et al.*, 1977). Only one ear of each mouse was treated. Irradiation was given with 250 kV X rays, HVL 1.2 mm Cu, at a dose rate of 3.6 Gy/min. Further details of the methods used are described elsewhere (Law *et al.*, 1977).

RESULTS

Heat alone

Severe heat treatment alone (for example 43.5°C for one hour) caused necrosis of the ear during the first few days after heating. This response was expressed as the percentage of mice which showed signs of developing necrosis. The time of onset of necrosis after various treatments is shown in Fig. 1.

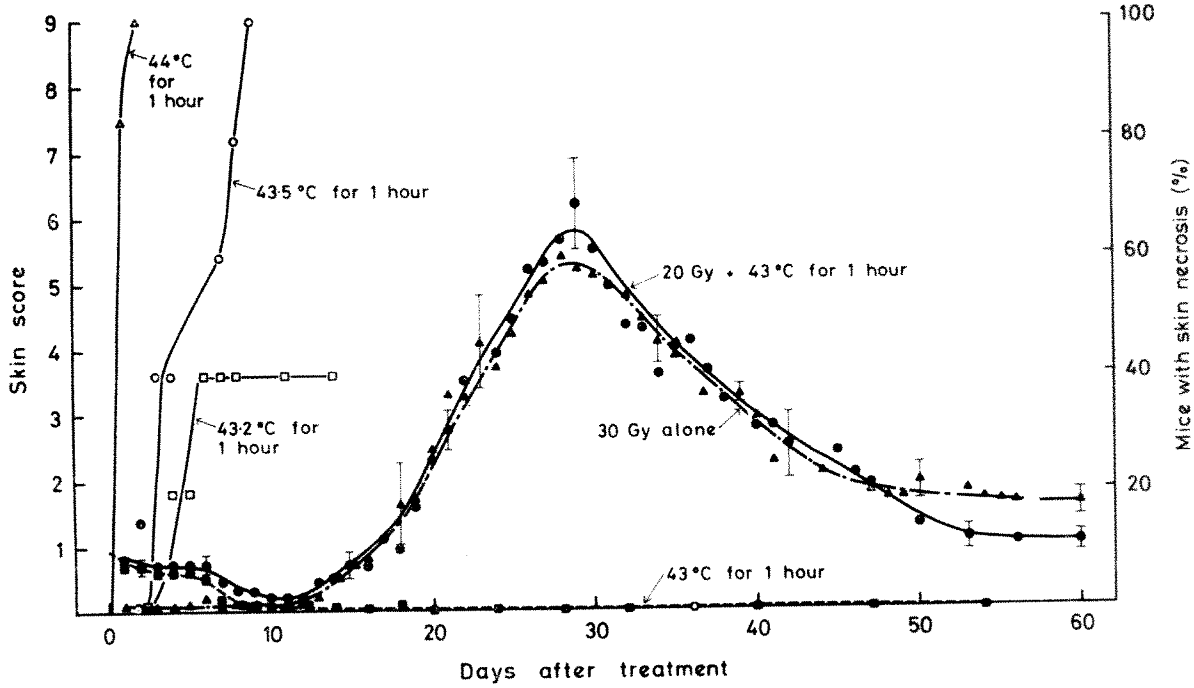

FIG. 1.

The response of the mouse ear to various treatments.
△○□ Necrosis (right ordinate) after severe heat treatment (6–12 mice for each treatment).
■ The skin reaction (left ordinate) after mild heat treatment (12 mice).
▲ The skin reaction (left ordinate) after X rays alone (6 mice).
● The skin reaction (left ordinate) after X rays followed immediately by heat (6 mice).

Both the rate at which necrosis developed and the number of mice which ultimately showed necrosis depended on the severity of the heat treatment. There was no further change after 14 days and therefore the index of the response to a given heat treatment was taken to be the percentage of animals with necrosis by 14 days. As soon as a mouse showed signs of necrosis it was sacrificed.

Heating times ranging from 15 to 120 minutes were investigated. At each treatment time the temperature was varied such that the percentage of mice developing necrosis ranged from 0 to 100%. The results are shown in Fig. 2 in which the percentage of animals with early skin necrosis is plotted as a function of temperature for various heating times. It can be seen that for all treatment times, once a threshold had been reached, the effect of increasing the temperature was dramatic. An increase of only 0.5°C was required to increase the probability of necrosis from 0 to 100%. It is also seen in Fig. 2 that as the time was increased the temperature required to produce any level of necrosis was reduced. This is shown in Table I in which the temperature to produce necrosis in 50% of the mice is given for each heating time.

Heat and irradiation

Radiation alone caused erythema and desquamation which began during the third week after exposure. These acute skin reactions were scored for two months after irradiation using an arbitrary numerical scale. Scores up to two indicate degrees of erythema and scores of three to nine represent increasing areas of moist desquamation (Law *et al.*, 1977). The time course of the response is shown in Fig. 1.

Mild heat treatment alone (≤43°C for one hour, or equivalent) had no detectable effect during the time that the radiation response was observed (*i.e.* 10–50 days). When heating was given immediately (*i.e.* two minutes) after irradiation, the response was not qualitatively different from that due to X rays alone. However, the dose of radiation required to cause a given reaction was smaller for the combined treatment than for X rays alone, as illustrated in Fig. 1.

In order to determine the relationship between time of heating and temperature to produce a given enhancement of radiation damage, 216 mice were all given the same dose of X rays followed two minutes later by hyperthermia. Heat treatment was given for

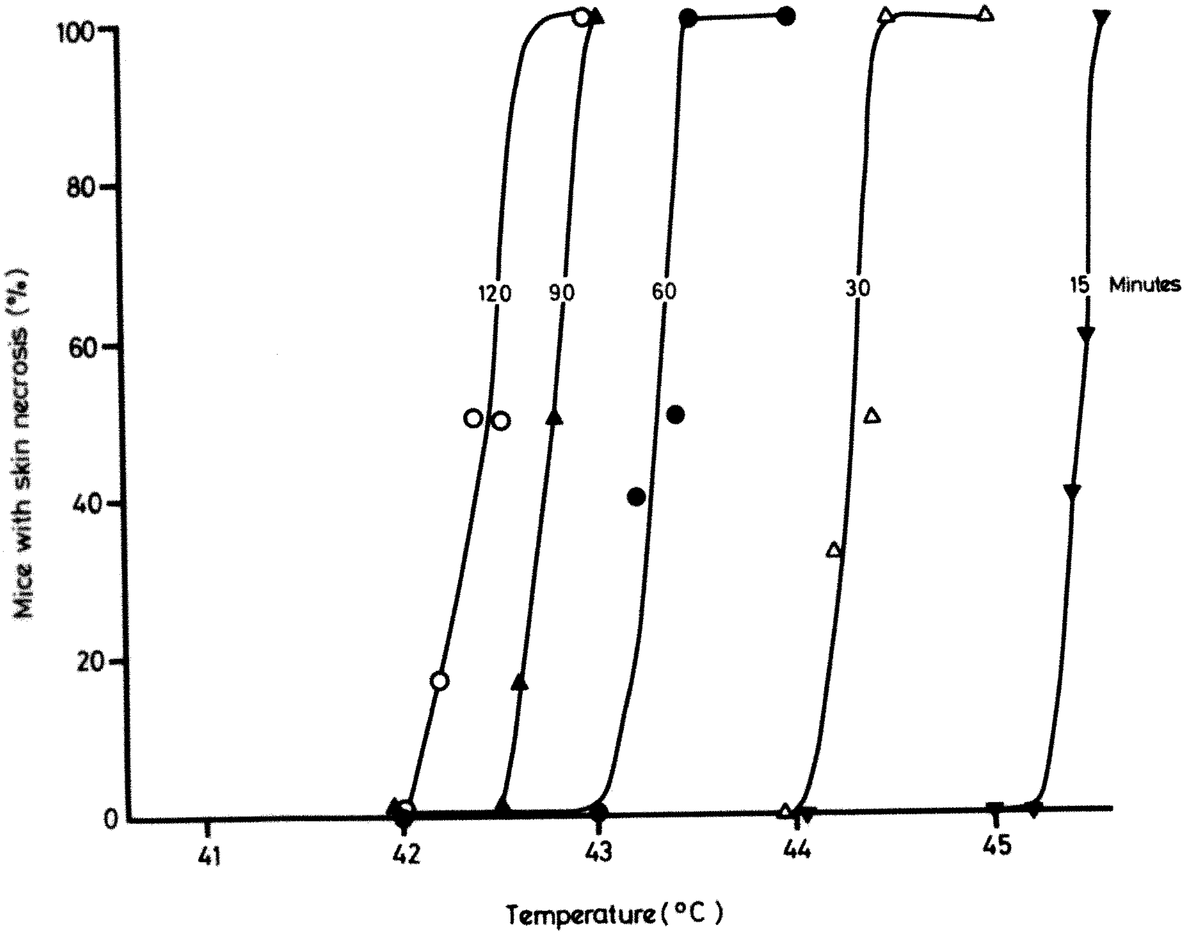

Fig. 2.

Necrosis of the mouse ear after severe heat treatment alone. The percentage of mice showing signs of necrosis is plotted as a function of temperature for various heating times.

TABLE I

Effect of heat alone

Heating time (min.)	Temperature for 50% probability of necrosis (°C)
120	42.5
90	42.8
60	43.3
30	44.3
15	45.5

different lengths of time ranging from 7.5 to 240 minutes, and the temperature was varied for each heating time. This was done with two standard doses of X rays, 15 Gy and 17.5 Gy, which alone only cause erythema. The response was expressed as the maximum score or as the average reaction during ten to 50 days after treatment. It has been shown that the maximum score was numerically twice the average reaction (Law *et al.*, 1977). For each treatment time, a curve was constructed to relate either maximum score or average reaction to post irradiation temperature. An example is given in Fig. 3 which shows the maximum scores for various heat treatments after all mice had received an X-ray dose of 15 Gy. Similar curves were obtained when average reactions were used. All the hyperthermia treatments given slightly enhanced the radiation effect, but with little dependence on the degree of heating until a threshold was reached. The effect of increasing temperature was then such that an increase of about 1.0°C was required to increase the reaction from about three (first signs of skin breakdown) to a severe reaction of five (desquamation over more than half the outer surface of the ear). Similar results were obtained for 17.5 Gy, except that for a

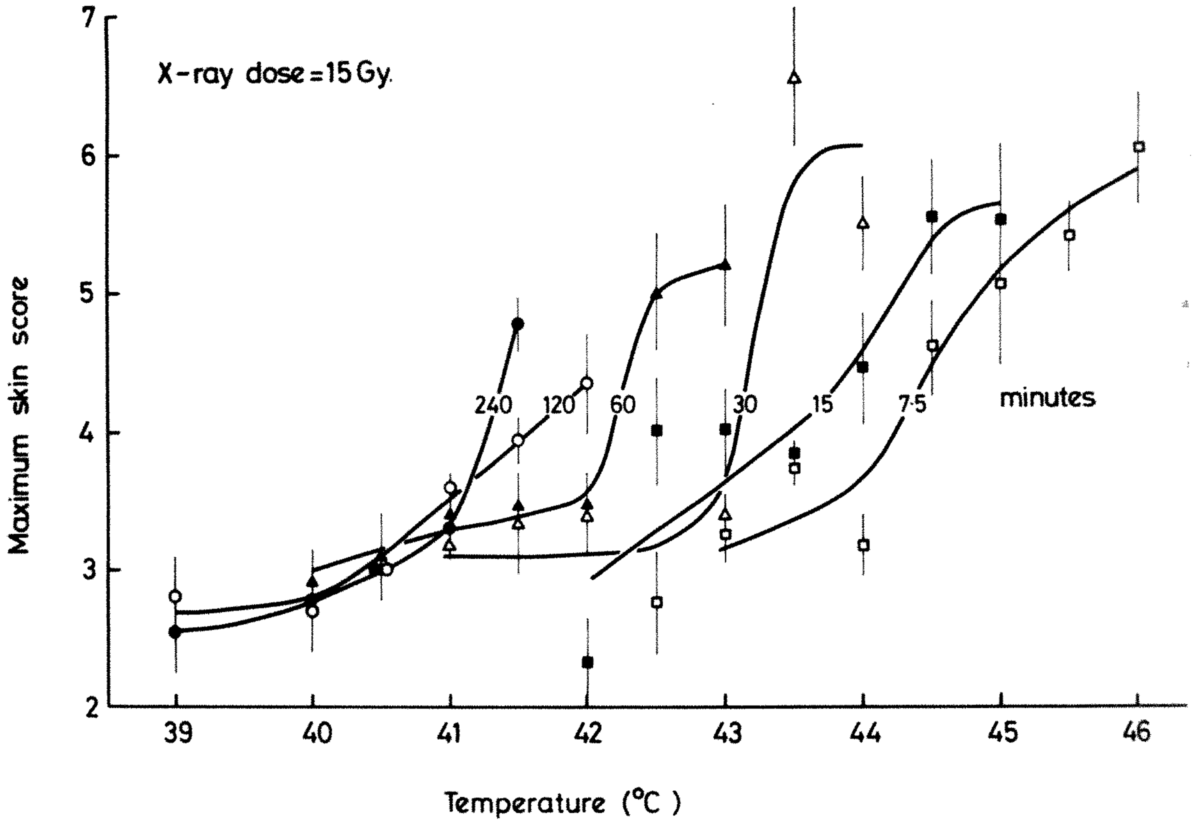

FIG. 3.

Thermal enhancement of the radiation response of the mouse ear. The maximum skin score recorded during ten to 50 days after an X-ray dose of 15 Gy is plotted as a function of temperature for different heating times. Hyperthermia was given two minutes after the end of irradiation. Each point represents the mean for four to six mice and vertical lines indicate standard errors. An X-ray dose of 15 Gy alone only caused erythema (scores of less than two).

TABLE II

THERMAL ENHANCEMENT OF THE RADIATION EFFECT

Heating time (min.)	Temperature, °C					
	15 Gy*		17.5 Gy†			
	Maximum score = 4	Average reaction = 2	Maximum score = 4	Average reaction = 2	Maximum score = 5	Average reaction = 2.5
240	41.27	41.45	40.85	40.7	41.27	41.12
120	41.6	41.67	40.5	40.2	41.27	40.75
60	42.17	42.1	40.87	40.6	41.6	41.15
30	43.1	43.15	42.35	41.9	43.6	42.65
15	43.5	43.1	42.4	—	43.15	42.90
7.5	44.25	44.15	43.2	42.87	44.25	43.30

*15 Gy alone causes erythema, maximum score = 1.2 ± 0.2
average reaction 0.27 ± 0.05.
†17.5 Gy alone causes erythema, maximum score = 2.5 ± 0.5
average reaction 0.70 ± 0.01.

given heating time the threshold was at a lower temperature, e.g. 40.5°C for one hour.

The relationship between heating time and temperature was determined at several levels of damage for both 15 Gy and 17.5 Gy. The results are given in Table II.

DISCUSSION

The results given in Tables I and II are shown graphically in Fig. 4. It can be seen that the relationship between heating time and temperature was different for the effect of heat alone compared with that for thermal enhancement of radiation damage. For necrosis caused by heat alone the time required to produce a given level of damage had to be reduced by a factor of two for a rise in temperature of 1°C. For heat combined with X rays the time required to produce a given enhancement of the radiation effect had to be reduced by a factor of three for a rise in temperature of 1°C.

The relationship between heating time and temperature (Fig. 4) shows how a given heat treatment may be changed without altering its effect, but gives no information about the magnitude of the biological effect caused by a small deviation in either heating temperature or time. The results given in Figs. 2 and 3, however, show that small differences in temperature may have a marked effect on the response of hyperthermia either alone or combined with X rays. For heat alone (Fig. 2) at the limit of tissue tolerance, an increase of only 0.5°C (equivalent to an increase in heating time by a factor of 1.4) was required to increase the probability of early necrosis from 0 to 100%. Morris *et al.*, (1977) have reported a similar result in the baby rat tail where an increase in heating time of 20% (equivalent to 0.3°C) was required to produce 100% necrosis. For mild heat treatments which only enhance the radiation effect (Fig. 3) the maximum skin score was increased from about three to five for an increase of about 1°C above the threshold temperature for any given heating time. From radiation dose effect curves (Law *et al.*, 1977), this is equivalent to increasing the dose of X rays alone from about 20 Gy to 25 Gy, *i.e.* by about 25%. A similar conclusion may be reached using thermal enhancement ratios (TER). Data for a number of rodent tissues shows how the TER increases between 41°C and 43°C for one hour (Law *et al.*, 1977). At 42°C for one hour a change in temperature of 1°C is equivalent to a change in X-ray dose of 26%. Therefore an increase in temperature of 0.5°C (or an increase in time in this case by a factor of 1.8) is equivalent to a 13% increase in X-ray dose and may increase the tissue reaction to combined treatment above that considered to be the radiation tolerance.

Some information about the kinetics of heat inactivation may be obtained using the Arrhenius equation (Henriques, 1947; Westra and Dewey, 1971) in which the activation energy (E) is given by

$$k = Ae^{-E/RT}$$

where k = reaction rate, R = gas constant and T = absolute temperature. In the present experiments the reaction rate of some critical process may be taken to be proportional to the reciprocal of the heating time. Activation energies (Table III) were calculated from the slopes of regression lines relating temperature to reaction rates for the effects of heat alone and of heat combined with X rays (*e.g.* Fig. 4). For heat alone only one end point, namely necrosis in 50% of the ears heated, was used. For heat combined with X rays a number of levels of skin reaction were used. Standard errors were estimated from the variances on the slopes of the regression lines.

The value of 580 kJ/mole calculated from the present data for the effect of heat alone is within the

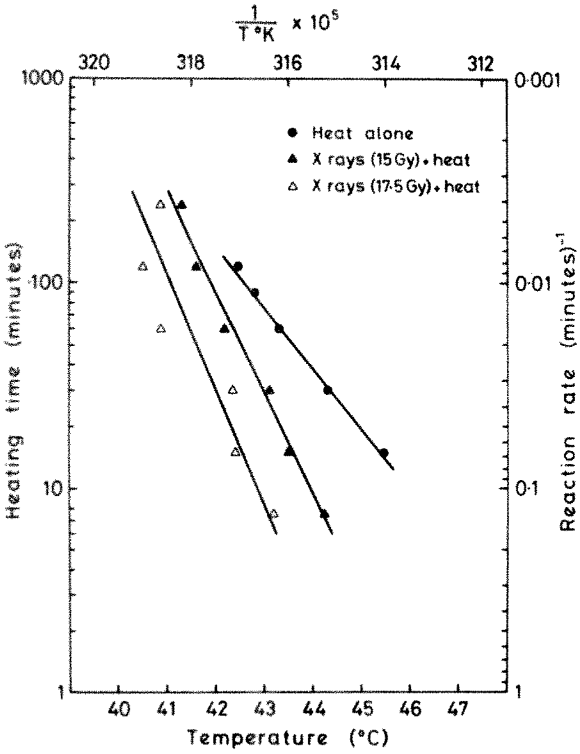

FIG. 4.

The relationship between heating time and temperature for the response of the mouse ear to heat applied alone or combined with X rays. For heat alone the isoeffect was necrosis in 50% of the ears treated. For heat given immediately after X rays the isoeffect was a maximum score of four. Different isoeffects gave lines parallel to those shown.

TABLE III

Activation energies

Treatment	Endpoint	Activation energy kJ/mole
Heat alone	Necrosis (50%)	583 ± 20
15 Gy + heat	Maximum score = 4 Average reaction = 2	940 ± 57 1074 ± 135
17.5 Gy + heat	Maximum score = 4 Average reaction = 2 Maximum score = 5 Average reaction = 2.5	1063 ± 222 1110 ± 309 913 ± 154 1069 ± 226
X ray + heat	Mean of all estimates	1030

range of values (500–750 kJ/mole) obtained for a number of mammalian cells *in vitro* and tissues *in vivo* (Henriques, 1947; Westra and Dewey, 1971; Morris *et al.*, 1977). These values are comparable with those for the denaturation of enzymes and proteins (480–840 kJ/mole) (Johnson *et al.*, 1954), in agreement with the suggestion that protein denaturation is the primary cause of thermal injury (Henriques, 1947; Westra and Dewey, 1971).

The various estimates of activation energy for the effect of heat combined with X rays (Table III) are not significantly different from each other, with an average of 1030 kJ/mole. They are, however, significantly different from the estimate for the response of the ear to heat alone, which suggests that the two modalities act by different pathways. This is hardly surprising in view of the qualitative differences between the responses (Fig. 1). Severe heat treatment causes necrosis during the first few days, presumably due to intermitotic cell death, whereas mild hyperthermia enhances radiodermatitis which is the visible result of radiation-induced mitotic death (Withers, 1967; Denekamp *et al.*, 1969). Activation energies in the range of 480–840 kJ/mole are often associated with protein denaturation by heat (Johnson *et al.*, 1954) rather than with damage to DNA since values for strand scission in DNA (Eigner *et al.*, 1961), loss of transforming activity of bacterial DNA (Ginoza and Zimm, 1961) and depurination of DNA (Greer and Zamenhof, 1962) are in the range of 100–150 kJ/mole. In view of the errors on the estimates given in Table III, the activation energy of about 1000 kJ/mole for combined heat and radiation is consistent with the suggestion that protein denaturation is also a factor in the potentiation of radiation damage by heat. It may be that thermal enhancement is at least partly affected by inhibition of enzymes involved in repair processes (Bronk *et al.*, 1973) whereas injury by heat alone is due to denaturation of some other enzymes. However, in our present state of knowledge this is only speculation.

Activation energies for the effects of heat alone and heat combined with ionizing radiation have also been estimated by Loshek (1976) for cells *in vitro* and by Robinson *et al.* (1977a and b) for mouse tumours *in vivo*. With Chinese hamster cells, Loshek (1976) obtained a value for the activation energy for heat alone which was not significantly different from that for ear necrosis presented here, but the value for combined treatment (380 kJ/mole) was less than that for heat alone (640 kJ/mole). In these *in vitro* experiments, however, hyperthermia was given 100 minutes after exposure to X rays. Recent results have shown that the enhancing effect of heat is progressively lost as the time between irradiation and hyperthermia is increased. By 100 minutes there would be little enhancement in some systems (Gerweck *et al.*, 1975; Henle and Leeper, 1976; Stewart and Denekamp, 1977; Law *et al.*, 1977, Myers and Field, 1977). In addition, using cell survival as the end point, Loshek was unable to discriminate between two qualitatively different effects for the two treatments as can be done *in vivo*. Therefore the present results and those of Loshek may not be comparable.

Robinson *et al.* (1977a and b) investigated the delay in regrowth of mammary tumours after various treatments. For heat alone an increase in heating time by a factor of two was equivalent to a temperature rise of 0.76°C. This gives an activation energy of ~760 kJ/mole, which is just within the range of values obtained for the effect of heat on a number of other *in vitro* and *in vivo* systems (Morris *et al.*, 1977). For heat given simultaneously with low dose radiation, increasing the heating time by a factor of two was equivalent to a temperature increase of 0.42°C, giving an activation energy of ~1370 kJ/mole. This value is somewhat greater than that obtained for the mouse ear (present results), but the two *in vivo* systems gave comparable results in that the activation energy for the combined treatment was greater than that for heat alone.

Conclusions

1. Severe heat treatment of the mouse ear caused necrosis during the first few days after heating. Mild heat treatment, which caused little effect alone, enhanced the response to radiation which occurs during ten to 50 days after treatment.

2. For heat alone, isoeffect curves showed that the time required to produce a given level of necrosis

had to be reduced by a factor of two for a rise in temperature of 1°C. For heat combined with X rays the time required to produce a given level of radiodermatitis had to be reduced by a factor of three for a rise in temperature of 1°C.

3. For heat alone at the limit of tissue tolerance, an increase in temperature of 0.5°C, or an increase in heating time by a factor of 1.4, resulted in complete necrosis of the heated volume. For mild heat treatment which only enhanced the radiation response, an increase in temperature of 0.5°C, or an increase in heating time by a factor of 1.8, was equivalent to an increase in X-ray dose of about 13%.

4. Activation energies were calculated to be 580 kJ/mole for necrosis after heat alone and 1030 kJ/mole for thermal enhancement of radiation damage, suggesting that different processes may be involved in the two responses.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

TELEVISON FLUOROSCOPY—A NECESSITY OR AN UNSUPPORTABLE LUXURY?

In your July edition you published a letter by Samuel and Philp (1977) regarding the above subject. We would like to take this opportunity to reply and to bring up to date the situation described in their letter.

The introduction of high resolution image intensifier in the beginning of this decade certainly brought about advantages for the 70 mm and 100 mm indirect technique (Pfeiler and Linke, 1977). However, the X-ray television picture can also profit from the high resolution image intensifier despite the fact that the conventional TV system cannot reproduce the high quality output picture from the intensifier without noticeable loss (Haendle, 1975; Delgambe, 1975).

This has led to the development of high resolution television systems in which the individual components such as optics, TV camera, tube, video amplifier and monitor systems have all been considerably upgraded (Haendle and Horbaschek, 1976). In addition, the number of lines in the TV systems has been doubled. As a result of all these improvements it can be seen in practice that the new high resolution systems available today produce a considerably improved resolution capability even when using small screening dose values (accepting significant quantum noise).

One must also consider that the use of a television viewing system is beneficial to the radiologist because the contrast of the TV picture is basically higher than that of the original image intensifier output picture. The radiologist's job is therefore simplified. Another point must also not be forgotten, that is that remote control tables which offer the examiner optimal radiation protection could not exist without TV.

Yours, etc.,
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THE EDITOR—SIR,

^{99}Tc^{m}-FIBRINOGEN AS A THROMBUS-IMAGING AGENT

The early detection of venous thrombosis of the leg by use of the (Flanc *et al.*, 1968; Kakkar, 1972; Browse, 1972; Skillman, 1974) radiofibrinogen uptake test has been shown to be very accurate. In an effort to use nuclear medical imaging equipment for clot visualization, we have investigated the *in vivo* use of ^{99}Tc^{m} labelled fibrinogen in rabbits. The preparation of ^{99}Tc^{m}-fibrinogen by electrolytic reduction of the pertechnetate at pH 1–3 using zirconium electrodes (Wong and Mishkin, 1975), and at pH 6 using tin electrodes (Harwig *et al.*, 1976) in the presence of fibrinogen has been reported. Our ^{99}Tc^{m}-fibrinogen was prepared by Sn^{++} reduction of the pertechnetate at pH 8–9 in the presence of fibrinogen (Kabi) using a carbonate/bicarbonate buffer (the use of a phosphate buffer (Harwig *et al.*, 1976) produces an undesirable Tc-monophosphate label). Routine quality control was performed using TLC-chromatography (silica gel, 80% methanol/water as solvent, protein localization using ninhydrin and autoradiographic localization of activity). Thrombi were experimentally produced in the neck vein of rabbits using the method of Siegel *et al.* (1972), in all cases an incision was made on the left side of the neck as control.

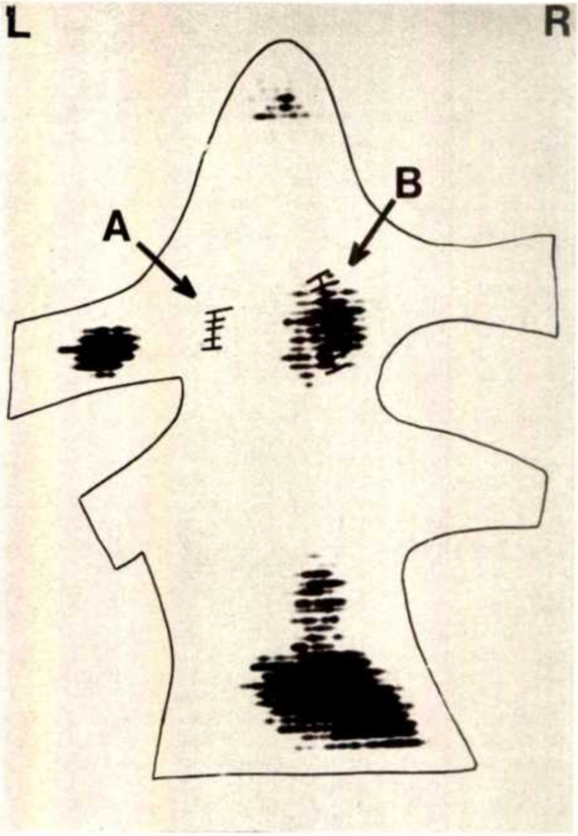

FIG. 1.
Scintigram of a rabbit

Figure 1 shows a scintigram of a rabbit one day post-operation, six hour post-injection of 200 μCi of ^{99}Tc^{m}-fibrinogen (the head, ears, front legs and upper part of the body may be seen). A is the control incision and B is the experimentally produced clot (sodium perchlorate was administered before injection of pertechnetate to block the thyroid).

The liver was found to be the "hottest" organ with no noticably high gut uptake.

Re-examination of the same rabbit six days post-operation demonstrated isotope uptake on a non-active clot.

Yours, etc.,
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THE EDITOR—SIR,

CURVE STRIPPING OF THE THIRD PHASE OF THE RENOGRAM IN ESSENTIAL HYPERTENSION

When there is no obstruction in the urinary out-flow tract, the third phase of the renogram indicates the rate at which the ^{131}I Hippuran is removed by the kidneys. Retention of Hippuran in the pelvis and ureteric peristalsis do not affect the third phase in normal cases. The shape of the third phase depends on the shape of the input of Hippuran and the spectrum of transit times through the kidneys (Britton and Brown 1971).

The third phases of 22 normal renograms were analysed by an exponential peeling technique, and two exponents were seen with mean values of 0.52 ± 0.159 and 0.08 ± 0.032. (Fig.1).

Twenty renograms of essential hypertension were analysed in the same manner and the third phase of these renograms were found to contain only a single exponent with a decreased mean value of 0.05 ± 0.022. (Fig.2).

This simple stripping method corroborates the finding of bimodal excretion in normal renograms by deconvolution analysis (Britton and Brown 1975). The two modes are due to two populations of nephrons, namely the cortical and juxta medullary groups. In essential hypertension, blood flow through the cortical nephrons is reduced due to auto regulation. This causes the apparent disappearance of one exponent in cases of established hypertension.

A graphic proof of this phenomenon has been shown by Kinoshita *et al.*, (1974) where the size of the kidney scan is reduced within a minute when the faster mode of excretion by the cortex is complete. The same authors have also found a preferential reduction of cortical perfusion in essential hypertension.

It is also strange that such a perfect fit of one or two exponents is obtained in the third phase even without blood background subtraction. This may be due to the fact that the slope of the blood background is equal to one of the exponents.

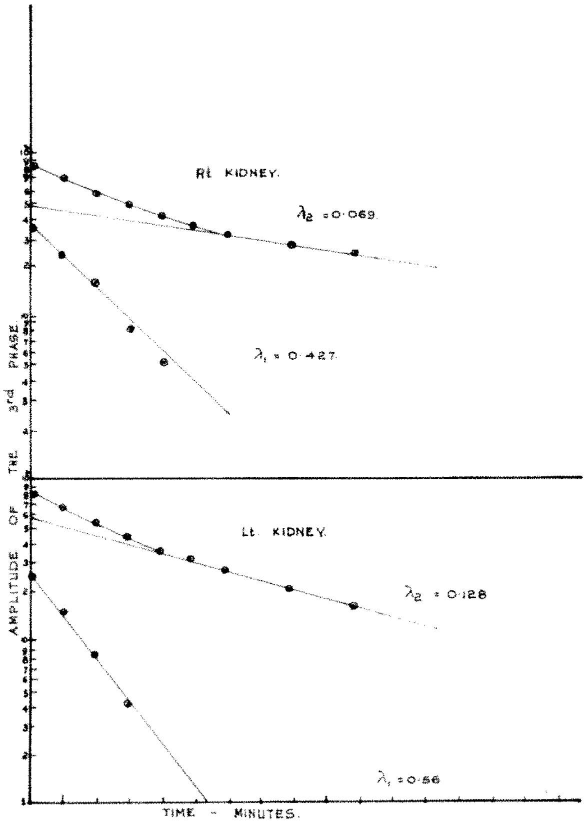

FIG. 1.

Exponential peeling of normal renogram showing two exponents.

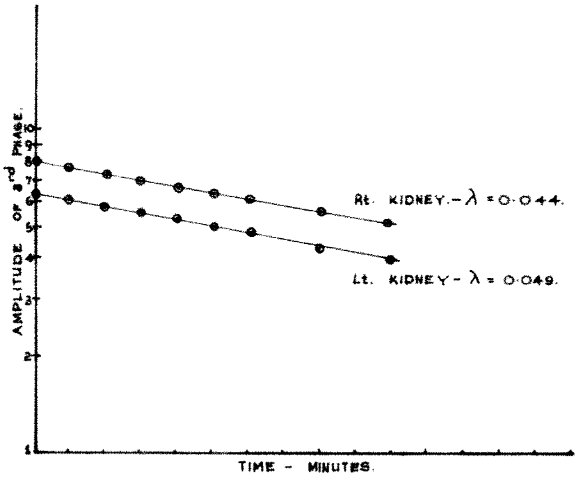

FIG. 2.

Exponential peeling of the renogram in a case of essential hypertension.

The clinical implication of this finding can be significant if the changes are reversible and pressure-dependant.

Yours, etc.,
C. RETHINASABAPATHI,
K. R. RAJAGOPALAN,
A. GAJARAJ,
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THE EDITOR—SIR,

TISSUE SUBSTITUTE MATERIAL "MIX D"

It was gratifying to learn from Dr. David White's letter in the August issue of your Journal (White, 1977), that Mix D (Jones and Raine, 1949) still remains among the most popular of the tissue substitutes. This wax is no longer available commercially, and for this reason I included details of its composition and method of preparation among the items listed in the recently revised edition of the *Radiation Dosimetry Data Catalogue*, published by the International Atomic Energy Agency (I.A.E.A., 1976).

Incidentally, this catalogue may be obtained free of charge on application to the Dosimetry Section, Department of Research and Isotopes, I.A.E.A., P.O. Box 590, A-1011, Vienna, Austria.

Yours, etc.,
D. E. A. JONES.

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THE EDITOR—SIR,

CORRECTIONS FOR HUMIDITY

In his letter to the Editor of THE BRITISH JOURNAL OF RADIOLOGY, Wheeler (1977) claims that the correction factor proposed by Wyckoff and Attix (1957) for humid air in an ionization chamber is incorrect. He states that the factor should be

$$\frac{273.2}{T}\left(\frac{P-0.3783\,P_1}{760}\right)\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(1)$$

instead of

$$\frac{273.2}{T}\left(\frac{P-0.238\,P_1}{760}\right)\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$$

where P_1 is the vapour pressure (in mm of mercury) of the water in the air.

It is Wheeler's factor, expression (1) above, that is the incorrect one, however, because his factor merely gives the ratio of *mass* densities (of the moist air in the ionization chamber relative to dry air at standard temperature and pressure). As Wyckoff and Attix (1957) clearly pointed out, ionization produced in a chamber depends upon the *electron* density present, and also upon $\overline{W}$, the mean energy expended in the gas per ion pair formed. The information available at that time on $\overline{W}$, used to weight the calculated electron densities in moist air, does indeed yield the correction factor (2) proposed by Wyckoff and Attix.

It may be of interest that, more recently, experiments done by Niatel (1969, 1975), Guiho *et al.* (1974), Referowski (to be published) and Hofmeester and Somerwil (to be published) indicate a different behaviour of $\overline{W}$ for moist air from that assumed by Wyckoff and Attix (1957). All these recent experimental determinations of the influence of water vapour on the ionization of air, both in free-air chambers and in cavity chambers, have shown consistent results that can now be used in making corrections for humidity.

Yours, etc.,
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Proceedings of The British Institute of Radiology

Joint radiological meeting—Leeds

Abstracts of papers presented at The British Institute of Radiology and Royal College of Radiologists meeting held on September 24 and 25, 1976 at Leeds University

Diagnostic Session

Portal hypertension—medical aspects, by M. S. Losowsky.
The surgical management of portal hypertension, by D. R. Giles.
Arterioportography, by H. Herlinger.
Transhepatic portal catheterization, by A. Lunderquist.
Transhepatic and intravenous cholangiography in jaundiced patients, by G. J. S. Parkin.
EMI whole body scanner in liver imaging, by L. Kreel.
The compleat angler—arteriography improved, by P. G. Keates.
Radiology and breast cancer (Glyn Evan Memorial Lecture of the Royal College of Radiologists), by Professor A. P. M Forrest (*no abstract received*).
Evolution of bone disease in chronic renal failure, by P. J. A. Robinson.
The role of radiology in the assessment of bone mass, by A. Horsman and B. E. C. Nordin.
Visual thresholds in radiology, by G. A. Hay.
Test objects for X-ray television, by N. J. Coleman.
Premedication for peripheral arteriography, by J. N. Glanville.
Premedication and anaesthesia for neuroradiology, by D. G. McDowall.
Cervical myelography with metrizamide, by J. T. Lamb.
Does fetal irradiation cause childhood malignancies?, by P. R. J. Burch.
Small bowel examination, pharmaco-radiological aspects, by L. Kreel.
The small bowel meal, by D. J. Lintott.
The small bowel enema, by M. J. Noakes.
The air contrast small bowel enema, by J. F. Dyet.
The two-film barium meal in the exclusion of childhood coeliac disease, by S. E. W. Smith.
The value of a normal pancreatic arteriogram in clinically suspected pancreatic carcinoma, by D. Finlay.
Projections in congenital heart disease, by J. B. Partridge.

PORTAL HYPERTENSION—MEDICAL ASPECTS

By M. S. Losowsky

Department of Medicine, Leeds University
(St. James's Hospital)

Portal hypertension is not a diagnosis. The reason for the portal hypertension must be established. The most important decision is whether or not there is concomitant chronic liver disease.

Presenting features requiring therapy include bleeding oesophageal varices, ascites and hypersplenism.

Bleeding oesophageal varices are by far the most common and most important complication of portal hypertension requiring therapy. In a patient with gastrointestinal bleeding and oesophageal varices there is approximately a 50% chance that the bleeding is not from the varices. Thus the first essential is to be sure that the bleeding is from the varices.

Medical therapy for bleeding oesophageal varices includes, of course, supportive therapy and blood transfusion and a judicious avoidance of sedatives and other drugs which may make the situation worse. In the patient without chronic liver disease the prognosis is good and complications are much less frequent than when liver disease is present. In the patient with liver disease particular attention must be paid to the prevention of encephalopathy.

Medical measures directed at stopping bleeding from oesophageal varices include balloon tamponade, intravenous vasopressin and intra-arterial vasopressin. Results of these procedures must be assessed using the same critical standards as are applied to the assessment of the results of shunt surgery.

Other procedures which might be classified as medical rather than surgical include oesophagoscopic injection of varices, sclerosis of the left gastric vein by transhepatic cannulation, and several additional manoeuvres which have not found wide favour.

THE SURGICAL MANAGEMENT OF PORTAL HYPERTENSION

By G. R. Giles

Department of Surgery, Leeds University
(St. James's Hospital)

Surgical interest in this subject is directed towards the control of gastrointestinal bleeding and it is very rare to be asked to perform surgery for the management of hypersplenism or ascites. The surgeon may be involved in the emergency control of haemorrhage or later in the patient's illness when he may be asked to decompress the portal venous system under elective conditions.

Emergency surgical control can be attempted by a direct attack of the varices themselves or by an attempt at portal decompression as an urgent procedure. Where the latter course is envisaged, it is important to make the attempt quickly before the patient loses too much blood and hepatic deterioration begins. In these circumstances the radiologist may be asked to demonstrate the patency of the portal system in a patient who has recently bled and may rebleed during the examination. There is a need for adequate and continuing blood replacement within the X-ray Department and for all concerned staff to be immediately available. This

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approach to the emergency management of bleeding varices is not acceptable to all workers and is under evaluation.

There is a tendency for surgeons to avoid central portosystemic shunts such as the end to side or side to side portocaval shunts. This type of shunt certainly diverts all portal blood away from the liver and is associated with post-shunt encephalopathy in a high proportion of patients. Spleno-renal shunts and mesenteric-caval jump grafts have a lower incidence of encephalopathy and probably have equal decompression qualities. More specific decompression of the oesophageal varices without necessarily affecting portal flow is the concept of the latest type of shunt—the distal spleno-renal shunt. Though this shunt is able to deal with oesophageal varices, it has not been completely free from problems of technique nor from post-shunt sequelae.

ARTERIOPORTOGRAPHY

By H. Herlinger

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Contrast medium injections into the physiological channels to the portal venous system not only produce anatomical data in the arterial and venous pulses, but also allow some conclusions on flow dynamics. This combination is of particular value to the planning of shunt surgery.

Seventy-four examinations were analysed for this presentation, nearly a third of them having been done as emergencies during bleeding. Extrahepatic causes of portal hypertension were found in 21 patients (28%). The recognition of splenic vein occlusion may present difficulties, and a splenic artery clearance time prolonged to two seconds or more is helpful in support of this diagnosis.

Arterioportographic requirements can be expressed for specific surgical shunts and are intended to ensure the practicability and success of the operation. For a distal spleno-renal shunt these are splenic vein patency with adequacy of flow and a diameter of at least 12 mm, absence of any splenic encasement by fibrosis, presence of dilated short gastric veins, a patent left renal vein. Requirements for a meso-caval interposition shunt are superior mesenteric vein patency with an available segment at least 5 × 1 cm, absence of thrombus, inferior vena cava patency and an adequate pressure gradient from portal vein (measured as wedged hepatic pressure) to the inferior vena cava.

Absolute contraindications to any form of shunt are malignancy, hepatic or extrahepatic, and the occlusion of all major portal vein together with the absence of any suitably large collateral channel; relative contraindications are severe hepatic artery flow insufficiency and the presence of sub-hepatic caval hypertension.

The incidence of occlusion, presence of thrombus, size inadequacy and abnormality of flow in the major portal veins were presented.

TRANSHEPATIC PORTAL CATHETERIZATION

By A. Lunderquist

Department of Diagnostic Radiology,
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From 1973 to now, 270 percutaneous transhepatic catheterizations of the portal vein have been performed at the Department of Diagnostic Radiology in Lund, Sweden. In most cases the indication has been portal hypertension, in other patients liver metastases or pancreatic tumour were suspected. In patients with portal hypertension we have found this method extremely useful to chart the anatomy of portal-systemic collaterals, many of them not possible to demonstrate by other methods such as splenoportography or arterioportography. The technique for percutaneous transhepatic portography will be discussed and different common and uncommon portal-systemic collaterals were demonstrated.

TRANSHEPATIC AND INTRAVENOUS CHOLANGIOGRAPHY IN JAUNDICED PATIENTS

By G. J. S. Parkin

St. James's University Hospital, Leeds

In his monograph on intravenous cholangiography, Robert Wise (1962) assessed the success rate of the technique at 40% in patients with a serum bilirubin level between 2 and 3 mg% and at only 32% with levels between 3 and 4 mg %. When the serum bilirubin rises above 4 mg% most authors regard the procedure as contraindicated because of the very low success rate.

Over the last three and a half years at Leeds (St. James's) University Hospital, we have been using a technique of prolonged overnight infusion of 17 gm of Ioglycamide in all patients with serum bilirubin levels between 1.5 mg% and 10 mg%. The technique is based on that of Fuchs and Preisig (1975).

In our series of 81 patients, the overall success rate was 80%. When the serum bilirubin level was less than 4 mg% at the time of investigation the success rate was 90%; with little difference between jaundice due to parenchymal liver disease (86%) and that due to extrahepatic biliary disease (92%). With serum bilirubin levels in excess of 4 mg %, the overall success rate was 47%, but there was a dramatic difference between the success rate in the parenchymal liver disease (80%) and extrahepatic biliary disease (11%).

In the whole series of 65 diagnostic examinations a false negative diagnosis was made in two cases (3%) and a false positive diagnosis strongly suspected in two further cases.

In cases where the prolonged infusion technique fails or where further information about the biliary tree is required, the fine needle transhepatic cholangiography technique of Okuda *et al.* (1974) is employed. Examples of this now commonly employed technique were briefly presented together with suggested precautions to minimize any possible complications.

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EMI WHOLE BODY SCANNER IN LIVER IMAGING

By L. Kreel

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As with conventional radiology, a knowledge of the normal anatomy is extremely important in the interpretation of the results with computerized tomography.

The axial sections are viewed from below. The liver size and shape will change from section to section, depending on the level. Four representative levels are: (i) the right lobe near the diaphragm with the base of the lung visible; (ii) right lobe only below this with the spleen visible; (iii) right and left lobes with portal vein; (iv) Riedel's lobe.

Note the falciform ligament, gastro-hepatic ligament, portal veins, hepatic veins, inferior vena cava and caudate lobe of the liver. Without contrast medium the gall-bladder appears as a low density rounded area. With contrast medium it is very obvious.

Adjacent intercostal spaces not infrequently produce bands of low density. Streak artefacts due to movement in adjacent structures can also occur. The size and shape of the liver and spleen must also be noted, for instance in showing "atrophy" or "post-infarction" changes in the liver. Metastases in the liver can be shown when they are 1 to 2 cm in size. They may be small or large, single or multiple. Most metastases are hidden by contrast, apart from endocrine tumours such as gastrinomas (Zollinger–Ellison syndrome) or carcinoid cysts which tend to have a lower density than metastases and do not take up contrast. An abscess may have a similar appearance to a cyst, but hopefully the clinical context will be different, especially in relationship to choledochoduodenostomy. Multiple metastases may be discrete or merge into each other to give the liver a very patchy appearance. If calcification is present in metastases, these show up as very dense lesions.

Dilated bile ducts have a low density arborisation pattern, tapering towards the periphery of the liver. The cause of the obstruction, such as a tumour in the head of the pancreas and other effects, such as obstruction to the stomach may also be shown. Its value in cases of obstructive jaundice may, therefore, be considerable.

A liver infarct, if recent, has a low density and surrounding ascites are easily visible. Occasionally, the size, shape and position of calcification may be important, as in long-standing thrombosis of the inferior vena cava. Collateral vessels may also be shown.

A "fatty liver" can be diagnosed as it is of low density, in which the portal vein appears as a structure of higher than liver parenchymal density.

Gall-stones can be shown both with and without contrast medium.

The spleen size can be assessed and splenic enlargement can be distinguished from other tumours, from tumour infiltration of the peritoneum and from ascites.

Calcified splenic artery aneurysms and infarcts have also been shown, and although of no particular clinical significance, their appearances must be known, so as not to cause diagnostic confusion.

THE COMPLEAT ANGLER—ARTERIOGRAPHY IMPROVED

By P. G. Keates

The General Infirmary, Leeds

Radiology has been bedevilled by the difficulty of recording three dimensional anatomy on two dimensional film. "Two views at right angles" is a useful, crude principle to overcome this, but leaves the problem of obtaining the views for further discussion. The history of angiocardiography provides an example of the difficulties. A simple A.P. projection supplemented by a lateral view was obtained by use of a pair of rigidly fixed film changers. More subtly angled projections required rotation of the patient within the open box formed by the changers and either propping him inaccurately and insecurely on pads, or else strapping him in a cradle like a chicken on a spit. The particular anatomical difficulties and dangers of coronary angiography led to the introduction of flexibly mounted X-ray apparatus which moved around the patient, giving multiple projections without movement of the patient. This system depends on use of an image intensifier and the maximum field size is therefore severely limited so that it is not suitable for general angiography.

In 1971, planning a new angiography suite for the General Infirmary at Leeds, we had no difficulty in selecting flexibly mounted apparatus for the cardiac room but no manufacturer offered anything comparable for general angiography. We had to devise our own system and persuade the manufacturer to accept our proposals and assist on their detailed development. The outcome is a 35 × 35 cm Puck-U film changer plus a 6 in image intensifier mounted on one limb of a Philips U-arm, with the X-ray tube on the other limb. The patient lies on a specially modified step movement table with a 95 cm metal free end, cantilevered out from the support, around which the changer gyrates over an arc of 180 deg. The intensifier and the changer are motor driven and change places in less than 15 seconds so that fluoroscopy and film exposure are on the same axis.

The assembly has been in routine use for two years and all parts of the body between the crown of the head and the soles of the feet have been successfully and easily examined. The free choice of projections has allowed us to take a fresh look at our routine procedures. The new enthusiasm engendered in radiologists and radiographers has only been exceeded by the benefit to patients who have received better examinations with less distressful manipulation.

We are perhaps prejudiced but it does seem to us that at the moment this is the best available system. Strangely, we understand that by a small margin it is also the cheapest!

EVOLUTION OF BONE DISEASE IN CHRONIC RENAL FAILURE

By P. J. A. Robinson

Department of Diagnostic Radiology,
St. James's University Hospital, Leeds

Metabolic bone disease is a major problem in long-term treatment of chronic renal failure (CRF). To prevent patients being incapacitated by fractures, deformities and bone pain, early diagnosis and specific prophylactic measures are desirable. A study of several hundred skeletal surveys has shown that the earliest radiographical change in Leeds' patients is almost always sub-periosteal erosion. Healing of the erosions has rarely occurred with standard dialysis techniques alone. When 20 patients were exposed for six months to an elevated dialysate calcium concentration (1.75 mmol/l), two showed partial healing of sub-periosteal erosions. In others, however, erosions deteriorated and the incidence and severity of soft-tissue calcification was increased. Small doses of 1α–OH–cholecalciferol have produced healing of erosions in several patients but again there has been an increase in the incidence of soft-tissue calcification. Periosteal new bone appears relatively uncommonly in patients on regular dialysis alone but has developed frequently after starting therapy with 1α–OH–cholecalciferol.

THE ROLE OF RADIOLOGY IN THE ASSESSMENT OF BONE MASS

By A. Horsman and B. E. C. Nordin

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Morphometry of the second metacarpal has revealed that age-related bone loss is a universal phenomenon in man. Many other bones of the skeleton have been examined morphometrically, although few investigators have measured more than two sites. In order to characterize the aging skeleton, we now perform morphometric measurements at six sites. The results for a given subject together with densitometric data on the distal radius and ulna are presented as a map on which the bone size, mass and density at each site are related to expected values based on normative cross-sectional data.

It is also possible to detect the changes occurring at the cortical boundaries in the individual patient by radiographic morphometry of six metacarpals. Although in the majority of cases the rate of loss cannot be accurately determined unless the observation period is long (approximately five years), the technique is extremely useful for evaluating the effects of therapy in small groups of subjects. The beneficial effects of oestrogen and calcium therapy in normal post-menopausal women, and of vitamin D and calcium therapy in crush fracture cases, have recently been demonstrated in this way.

VISUAL THRESHOLDS IN RADIOLOGY

By G. A. Hay

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The radiologist's visual task is twofold: threshold detection and pattern recognition. Very little is known about the mechanisms of the latter; this paper is concerned solely with the former.

Many structures in radiographs and in X-ray television images are difficult to detect because they are either too small or too faint. Such image structures are in general of three kinds: (1) approximately circular, *e.g.* a kidney stone: (2) approximately linear, *e.g.* a blood vessel; and (3) an edge, representing the boundary between two regions of differing radiopacity.

The detectability of these image structures depends on: (1) their own characteristics, *e.g.* size and contrast; (2) the degradation processes in the imaging system, *e.g.* unsharpness (mtf) and noise; and (3) the mechanisms of visual detection.

An understanding of these processes is not only of great fundamental interest in relation to the visual system but is also of practical importance because it may influence: (1) the design of imaging systems; (2) the design of testing methods; and (3) the way in which radiologists use their systems.

In this paper, the influence of unsharpness (mtf), noise and contrast loss on the detectability of circular details, linear details and edges were briefly discussed.

TEST OBJECTS FOR X-RAY TELEVISION

By N. J. Coleman

Department of Medical Physics, Leeds University

When measuring the performance of X-ray television systems, the basic criterion should be the diagnostic effectiveness of the system in clinical use. However, this measurement involves such difficulties that alternative methods are required, such as measurements of the quality of the radiological image produced by the system.

There are several factors which degrade image quality, of which the most important are unsharpness, noise, contrast loss, non-linearity, geometrical distortion and lag. Besides acting individually, they also interact with each other in complex ways.

It would be desirable to measure each of these factors independently under standard conditions, but this cannot be done sufficiently well to obtain absolute values of system performance. However, by making only relative measurements on particular systems, a useful indication is obtained of deterioration in performance and the consequent need for adjustment. A set of three test objects was described which enables such relative measurements to be carried out by engineering staff in routine checks of the system.

(This work is supported by the Department of Health and Social Security.)

PREMEDICATION FOR PERIPHERAL ARTERIOGRAPHY

By J. N. Glanville

St. James's University Hospital, Leeds

Premedication for peripheral angiography under local anaesthesia should relieve the patient of pain, of anxiety, be of sufficient flexibility to allow for unexpected delays in commencing a procedure and have no unpleasant side effects.

Ativan (Lorazepam, Wyeth) is a drug of the Benzodiazepine group. It has greater amnesic and anxiolytic action, lasts longer, but is slower in achieving its effect than Valium. Ativan orally alone in increasing dosage was found to be effective at 4 mg in producing sedation, anxiolysis and amnesia, but there was no analgesia.

Oral Ativan was then combined with oral Pentazocine (Fortral) and 4 mg Ativan and 50 mg Fortral proved an effective premedication given an hour before attending the department. Ativan 3 mg and 30 or 60 mg Fortral given intravenously is even more effective and achieves its full effect within 30 minutes. Intravenous Ativan 3 mg may be also combined with 50 or 100 mg Fortral orally.

Ideally the patient should have 2 mg Ativan orally the night before and oral or intravenous Ativan together with oral or intravenous Fortral as premedication.

PREMEDICATION AND ANAESTHESIA FOR NEURORADIOLOGY

By D. G. McDowall

Department of Anaesthetics, Leeds University

The neuroradiological procedures for which general anaesthesia are commonly required include carotid and vertebral angiography and lumbar pneumoencephalography. Premedication can usually be omitted since many patients are drowsy and most of the others are not anxious about a neuroradiological investigation. Oral diazepam in the adult and oral trimeprazine in the child are suitable if indicated.

Patients presenting for angiography commonly have intracranial space-occupying pathology either in the form of tumour or cerebral oedema and the anaesthetic technique must be designed to avoid increasing intracranial pressure. Thiopentone, Althesin and fentanyl are the most suitable drugs when used during passive hyperventilation under the influence of a muscle relaxant. Halothane, ketamine and spontaneous ventilation should be avoided in this group.

Patients presenting for air studies by the lumbar route commonly do not suffer from major space occupation so that the anaesthetic problems centre around protection of the airway and maintenance of a satisfactory blood pressure. Though the problems are different the technique of controlled ventilation with nitrous oxide and oxygen and fentanyl most readily permits the maintenance of a satisfactory blood pressure in the sitting position. The alternative technique of sedation involving fentanyl and droperidol were described.

Proceedings of The British Institute of Radiology

CERVICAL MYELOGRAPHY WITH METRIZAMIDE

By J. T. Lamb

The General Infirmary, Leeds

Forty-five patients have undergone cervical myelography following the introduction of metrizamide (Amipaque), using a lateral cervical approach.

The technique was described with the aid of a short film and the relative merits and disadvantages of this method were briefly discussed.

DOES FETAL IRRADIATION CAUSE CHILDHOOD MALIGNANCIES?

By P. R. J. Burch

Department of Medical Physics, Leeds Univsrsity

Many investigators claim that obstetric X-irradiation of the fetus, involving doses of about 1 rad, increases the subsequent risk of all malignancies during childhood by a factor of about 1.5. Such claims have followed from surveys in which pregnant women were selected for X-ray examination for medical reasons. Correlation, however, is not necessarily causation. We are unable, as yet, to eliminate the possibility that the medical conditions that prompt selection might themselves be associated with an enhanced risk of childhood malignancy. From the observed correlation the rules of statistical inference allow us to advance only the tentative suggestion: fetal irradiation might cause childhood malignancies. Further independent evidence is needed to substantiate the causal claim. Ideally we should select *randomly* from the population of pregnant women one group which we would subject to obstetric X-ray examination and the other control group which would be spared irradiation. Because ethical principles prohibit such an investigation we have to resort to other approaches.

It was shown that: (i) studies of childhood malignancy in children who were irradiated *in utero* at Hiroshima and Nagasaki; and (ii) an analysis of the age at onset of childhood malignancies as found in the Oxford Childhood Cancer Survey, cast doubt on the validity of the causal claim.

SMALL BOWEL EXAMINATION, PHARMACO-RADIOLOGICAL ASPECTS

By L. Kreel

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The demonstration of macroscopic anatomy is the chief purpose of the barium study of the small bowel. Flocculation and segmentation can be a misleading feature in patients believed to suffer from malabsorption and should be avoided as far as possible as they interfere with the recognition of lumen surface abnormalities. Transit time does not normally influence diagnosis but affects the appearence of the normal loops of small bowel; they tend to be dilated with slow passage and contracted when passage is rapid.

The barium meal and follow-through examination can be utilized to provide at least preliminary diagnostic information concerning the small bowel, and it is a form of examination widely used throughout the country. The use of pharmacological agents is of considerable value as it enhances the potential usefulness of the investigation.

Many factors cause more rapid emptying of the stomach. These include large volume, hyperosmolar solutions, low temperature, cholinergic drugs and metoclopramide. All these have also been used for the more rapid examination of the small intestine and, in particular, the terminal ileum, Of these, metoclopramide is the most consistently effective, can be given orally and, in the doses used in radiology, produces no side effects.

Dilatation of the stomach and duodenum can be produced by anti-cholinergic drugs. In this country Buscopan and Antrenyl are most commonly used as they are short acting, but side effects are not uncommon. They should not be given to out-patients who have to drive themselves home as they can cause failure of accommodation. The follow-through examination will be markedly prolonged as these drugs slow the transit of barium through the small bowel. They are the drugs best used to distinguish an area of "spasm" from an organic lesion on barium enema examination.

The drug which at present is most appropriately used in radio-diagnosis of the small bowel and stomach is glucagon. In a dose of 0.1 mg intravenously it can be employed for the double contrast examination of the stomach and duodenum and after 15 minutes this effect changes to that of small bowel hurry. This means that a follow-through examination is possible in 60 to 90 minutes in the vast majority of patients. No side effects have occurred using this dosage in over 500 examinations, but it remains to be seen whether repeat injections can be given safely in view of the possibility of immune reactions.

THE SMALL BOWEL MEAL

By D. J. Lintott

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The small bowel meal has been shown to be a reliable, simple and acceptable technique for the routine investigation of the small bowel in a busy general department with a large "small bowel" load. It has both radiological and administrative advantages over the conventional follow-through examination and it avoids intubation.

The technique involves the use of a large (300–600 ml) volume of dilute (SG 1.3–1.4) isotonic stable barium suspension with the occasional assistance of "accelerating" drugs. A series of prone overcouch films is taken and fluoroscopic examination is performed as indicated.

From 1973 to 1975 a total of 1023 small bowel meals were performed at the General Infirmary at Leeds. Excluding post-operative cases without recurrent disease, 25% of examinations were abnormal including 108 cases of Crohn's disease, 50 cases showing evidence of malabsorption and 104 with other miscellaneous lesions. Three per cent were considered diagnostically inadequate.

Ninety per cent of the examinations were completed within two hours at an average cost of consumables of £3·50 per patient.

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THE SMALL BOWEL ENEMA

By M. J. Noakes

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The only report in the literature to compare, in the same patients, a duodenal intubation method for the radiological visualization of the small bowel (Sellink's modification) with the more familiar follow-through type of examination concludes that intubation gave significantly better visualization of jejunum and ileum except for the terminal ileum where no significant difference was found (Fleckenstein and Pedersen 1975).

An alternative method for the double contrast examination of the small bowel is described and has been in routine use at St. James's and Chapel Allerton Hospitals in Leeds for ten years. Following dietary restriction and the administration of a laxative the patient is given Metaclopramide 20 mg orally ten minutes before the examination. A grey "Kifa" catheter with a short flexible rubber tip is inserted to the duodeno-jejunal flexure, using a 205 guide wire to avoid buckling within the fundus of the stomach. Usually 100 to 160 ml of undiluted Micropaque is then injected and followed by up to 2000 ml of ½% Prepacol or Fybogel solution in order to propel the Micropaque to the caecum, give a uniform distension of the small bowel and provide double contrast with the Micropaque-coated mucosa. Large differences of density and lumen diameter seen when air is employed as the double contrast medium do not occur when a watery solution is used (Sellink, 1976).

The procedure is carried out under intermittent screening control and spot films are taken with and without compressing. The examination from the moment the injection of barium is started, takes usually ten to twelve minutes.

Normal upper limits of the lumen calibre are 4.5 cm in the upper jejunum and 3.5 cm in the distal ileum. Normal valvulae coniventes are 1 to 2 mm thick, show straight contours and slightly rounded corners at their base against the bowel wall; wall thickness is about 1.5 mm.

Normal appearances were illustrated and a few examples of disease were shown.

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THE AIR CONTRAST SMALL BOWEL ENEMA

By J. F. Dyet

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Following duodenal intubation, the tip of the tube lying in the third part of the duodenum, barium is injected down the tube at a steady rate of approximately 100 ml per minute until the head of the barium column reaches the caecum. This requires between 400 and 1000 ml of barium. The abdomen is screened intermittently and the progress of the barium column observed. Spot films are obtained of any lesion shown. At least two films are always obtained, one of the jejunal loops and a further film at the end of the barium injection, to show the whole of the small bowel.

Up to 800 ml of air is then injected. This bubbles rapidly through the barium giving a true double contrast effect. Spot films are taken as required. At the end of the examination the abdomen is examined under the intensifying screen using a wooden spoon to palpate and separate out overlapping loops. This ensures good visualization of the whole of the small bowel.

THE TWO-FILM BARIUM MEAL IN THE EXCLUSION OF CHILDHOOD COELIAC DISEASE

By S. E. W. Smith

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There is still need for a simple, reliable, out-patient test for the exclusion of untreated coeliac disease in children to avoid jejunal biopsy. This report describes prospective experience over five years to assess a two-film barium meal—two supine films, at 20 and 40 minutes after a drink of Raybar, with the child laid in the right prone oblique position after feeding. From these two films were measured (1) the bowel calibre ("positive" was above the high normal range of Haworth *et al.*, 1967); and (2) the transverse mucosal folds ("positive" was more than six large folds in at least three separate loops of bowel on any one film).

Negative meals were negative on both counts; marginal examinations were called positive.

Two hundred and eighty-seven two-film meals were examined in children between three months and ten years of age with a variety of gastro-intestinal symptoms and signs which might be attributed to coeliac disease. In 48 children with untreated coeliac disease there were only three (6%) who had negative two-film meals. Out of 287 children, 138 with negative meals could be excluded from further investigation. The test compares favourably in accuracy with other tests, apart from jejunal biopsy.

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THE VALUE OF A NORMAL PANCREATIC ARTERIOGRAM IN CLINICALLY SUSPECTED PANCREATIC CARCINOMA

By D. Finlay

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In England, between 1960 and 1970, there has been a one third increase in the number of pancreatic carcinomas reported and this trend is world-wide.

Arteriography is a valuable technique in the investigation of suspected pancreatic carcinoma. A sound knowledge of the anatomy of the arterial network within the pancreas and of the vessels which lead to it from the major surrounding arteries is as important as the ability to manipulate catheters.

We have, therefore, analysed 100 of our pancreatic arteriograms in respect of intrapancreatic vessels and have compared these with Michel's classic series of 200 cadaveric dissections; excellent correlation was found. We benefit diagnostically in three ways. We are able to look for neoplastic changes involving small vessels within the pancreas and will demonstrate pathological vessels more consistently. We can show the surgeon confidently intrapancreatic vessels which go to supply other organs, *e.g.* a replaced middle colic artery. Thirdly, we can demonstrate the supply to parts of the pancreas, and this is of relevance before pancreatic surgery is undertaken.

Differing signs of pancreatic carcinoma have been described by different authors. We believe that in the pancreas itself adequate small vessel opacification will always demonstrate vascularity within the carcinoma and will allow angiographic diagnosis of a carcinoma at least 1 cm in diameter. Truly avascular carcinomas are found in the ampullary region and are really of bile duct origin. These may be symptomatic while still small and not be diagnosable angiographically. Small lesions near the main pancreatic duct may present with pancreatitis and their angiographic diagnosis may be very difficult. Any area of focal pancreatitis is indicative of carcinoma, unless otherwise explained.

An adequate pancreatic arteriogram excludes the presence of pancreatic carcinoma except in the presence of obstructive jaundice or pancreatitis.

PROJECTIONS IN CONGENITAL HEART DISEASE

By J. B. Partridge

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The ease and accuracy of interpretation of right or left ventricular angio-cardiography in congenital heart disease is increased, in almost all circumstances, by selecting the projection that profiles the interventricular septum (the axial view). Ventricular septal defects (which alone or with other malformations are found in half of all cases), the relationship of the great vessels to the septum in transposition and other construncal malformations, and the size and position of the atrioventricular valves are all best seen in this view. In the normal heart the axial view is 60 deg LAO.

The corresponding view on biplane equipment displays the ventricles in their long axis (the tranverse view.) This view is the best for the inflow and outflow tracts of each ventricle and for the evaluation of ventricular function and mitral or tricuspid regurgitation.

In both views the spine is projected clear of the heart, so improving clarity. The right and left pulmonary arteries are separated, and stenoses at their origins made clearer. An added cephalo-caudal tilt on the axial view is of use where more horizontal structures are of interest (*e.g.* the main pulmonary artery).

Therapy Session

A regional cancer organization, by C. A. F. Joslin.
Carcinogenesis in an industrial age, by M. Gronow.
Hypokalaemia and hypomagnesaemia as a mode of cancer therapy, by F. M. Parsons.
Tumour antigens and their implication in cancer screening and prevention, by J. P. Dickinson.
Multivariate analysis in breast cancer, by F. T. de Dombal.
Hyperbaric oxygen versus hypoxic cell radiosensitizers, by G. E. Adams.
A clinical appraisal of hyperbaric oxygen in head and neck cancer, by G. H. Berry.
A clinical appraisal of hyperbaric oxygen in cervix cancer, by A. J. Ward, B. Dixon and B. Stubbs.
Hypoxic cell sensitizers in clinical radiotherapy, by S. Dische.
The search for oxygen independence (neutrons, pi mesons etc.), by R. E. Ellis.
A clinical appraisal of neutron therapy, by Mary Catterall.
Lymphocyte chromosomes, banding and irradiation, by Gillian Kitchingman.
Tumour ploidy and proliferation state in relation to radiotherapeutic response, by B. Dixon.
Combination chemo- and radiotherapy of a transplantable, metastasizing tumour, by J. V. Moore.
Studies of bone structure and dosimetry of bone-seeking radionucludes. Some results and implications, by F. W. Spiers.
The dynamic aspects of bone tumours, by J. M. Fitton.
The place of radiotherapy for bone tumours, by L. A. Firth.

A REGIONAL CANCER ORGANIZATION

By C. A. F. Joslin

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One of the four experimental cancer organizations established by the DHSS in 1972 is based in Yorkshire. The primary purpose of the organization is to determine the value of introducing an advisory and co-ordinating service for those concerned with cancer management. This necessitates covering a whole range of interests including cancer prevention, early detection, cancer registration and statistics, treatment, supportive and continuing care, public and professional education and research.

To cover these interests some 18 different groups have been established. A number of these are disease orientated and primarily concerned with clinical management or research. Others are concerned with specialized facilities, *e.g.* cancer registration, cancer information services, occupational and industrial hazards, public and professional education etc. Since the object is to provide for all people in the region an equal and high standard of care, the part played by the organization in providing some of the means of achieving this has to be shown.

An essential preliminary, which has proven difficult, is to establish a base line of information. To simply register cancer is only a start to the problem and all existing resources have to be collated. Only by these means can the effect of changes be monitored and finally evaluated.

The chances of a successful outcome in favour of cancer organizations can only be achieved by the co-operation and enthusiasm of those taking part. It can be argued that this should be enough but without back-up support of various kinds to the different groups it is doubtful if more than a few could develop very far. It will, however, be for the assessment carried out after five years that the final decision on the future for cancer organizations will be made.

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CARCINOGENESIS IN AN INDUSTRIAL AGE

By M. Gronow

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Several famous cancer researchers have stated, "It is clear today that man and animals live in a sea of carcinogens". These may be (a) agents containing translatable information (*e.g.* viruses—well proven carcinogens in animals but not in man) and (b) agents not containing such information but capable of altering the information content of target cells (*e.g.* chemicals and various forms of irradiation). In some cases it is possible that a combination of these agents may lead to neoplastic transformation.

However, it is now becoming clear that up to 90% of all human cancers have a chemical involvement. Since the earliest documented cases of occupational cancers, such as the scrotal cancers of chimney sweeps (active agent 3, 4-benzpyrene) described by Percival Pots some 200 years ago, over 1000 chemicals have been shown to produce cancer in man and animals; many of them have been used and introduced by man into his environment.

Examples of the classes and types of chemicals involved will be presented with emphasis on those compounds used in industrial and manufacturing processes. Some of these hazards are probably still not identified due to the long latent period involved in the production of human tumours, as was the case with β-naphthylamines. Undoubtedly the most important chemical hazard, which seems to be an established part of modern life, is that of cigarette smoking. In addition it has been estimated that some 5000 new chemicals are being introduced annually in the form of new commercial products, chemicals, foods and drugs.

How can these compounds be screened for possible carcinogenic properties? To test a single suspect chemical can involve at least 500 animals, take on average three years to complete and sometimes cost in the region of £35 000. Clearly it is not economically possible to test every new chemical in this way and, if the substance is already in use, the delay involved could be critical. Therefore much recent research has been devoted to the development of rather more rapid screening procedures for potential carcinogens. The use of bacterial and tissue cell culture systems together with biochemical techniques for screening purposes will be described. In many cases a successful correlation has been obtained with these data and the results of animal feeding experiments. Unfortunately, despite the increasing usefulness of these pre-screen systems the animal test is still the only reliable guide. Hopefully when the true morphological and biochemical parameters of transformation have been evaluated animal tests will no longer be necessary.

HYPOKALAEMIA AND HYPOMAGNESAEMIA AS A MODE OF CANCER THERAPY

By F. M. Parsons

Renal Research Unit, Leeds General Infirmary

Regression of cancer of the bladder may occur after ureterosigmoidostomy; observations in the 1950s indicated that a specific biochemical imbalance could be responsible. In 1961–63 regression of cancer of bladder and breast was observed after Mg and K depletion had been achieved by dietary means. Difficulties of inducing adequate Mg depletion by diet and medication alone in patients with cancer caused us to abandon the project. In 1970, after *in vitro* studies, the investigation was restarted using haemodialysis to produce a controlled depletion of Mg and K in conjunction with a special, but rather unpalatable, daily diet, containing 2500 cal, 70 g protein but only 5 mg of Mg. Depletion of K, induced by dialysis, was accentuated using orally administered ion-exchange resins. Levels of K and Mg in the plasma of 2.5 and 0.1–0.2 mmol/l respectively were achieved and, surprisingly, were tolerated well by the patients, and no adverse symptoms developed provided the inevitable hypocalcaemia was corrected by haemodialysis (or parenteral infusion of Ca salts). The major problem, not yet surmounted, is to gain repeated access to the bloodstream to allow repetitive haemodialysis over an adequate time interval. Examples of regression of human cancers of lung, bladder and breast will be shown. Retardation of growth of transplantable tumours in the rodent in K and Mg depletion has also been demonstrated. Chemical analysis of normal tissue and transplantable tumours in the cation-depleted rodent indicate that malignant tumours probably have certain deficits of cellular function which adversely affect growth of the tumour. Our major clinical experience has been in inoperable carcinoma of the lung. Future investigation must include a more detailed study of the hypercatabolic state of some patients. The technique of K and Mg depletion has now been combined with high energy radiation in humans and with cytotoxic agents in animals. The complexity of the present regimens has not allowed worthwhile controlled trials but K and Mg depletion is a relatively "safe" clinical state and does not cause depression of bone marrow or other systems commonly associated with cytotoxic agents.

TUMOUR ANTIGENS AND THEIR IMPLICATION IN CANCER SCREENING AND PREVENTION

By J. P. Dickinson

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Brief consideration will be given to the origin, nature and function (other than as antigens) of the molecular components of tumours. Aside from those components determined by interaction with adventitious viral genomes, such materials elaborated by tumours are seen as inappropriate combinations of components characteristic of other stages of ontogenesis. The mechanisms through which an immune response to these inappropriately expressed materials and to normal tissue components may come about in the host will be examined. Particular consideration will be given to the role of the common tumour specific antigen (CTA).

The presence of inappropriately expressed materials in tumours may be monitored in two ways—by detecting specific immune response of the host to such materials or by detecting the presence of antigen in the host (tissues or body fluids). Specific examples of both types of approach will be examined (CTA, TPA, Makari test, CEA-Colon, AFP and melanoma antigen) and the problems of application and interpretation discussed.

Such immunological tests may be used for diagnosis, for monitoring the progress of disease or therapy, or for prognosis. No single test is likely to be useful in all of these applications; each test has operational limitations on specificity and sensitivity. (Specificity refers to the incidence of positive tests not due to the specific condition being sought.

Ideally, a range of test systems will be developed which will be capable of (i) detecting the presence of malignancy in individuals amongst the general population with a high degree of sensitivity, *i.e.* extremely few false negatives, but not necessarily very high specificity, *i.e.* a moderate number of false positives; (ii) in the absence of localizing clinical symptoms, excluding false positives and localizing the malignancy to a specific site or tissue for further investigation by physical methods and of indicating histological type; (iii) estimating tumour load; and (iv) monitoring the progress of therapy.

Because of the complex nature of the immune response and the nature of the antigens being reacted to, the possibility of predictably influencing the course of malignant disease by specific or non-specific immunotherapy is more remote. However, the specificity of the immune response may be useful in "homing" therapeutic agents.

MULTIVARIATE ANALYSIS IN BREAST CANCER

By F. T. de Dombal

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Research over the last few decades has clearly indicated that there is no single clinical attribute which can discriminate with complete accuracy between benign and malignant breast lesions or indicate with complete accuracy patients' prognoses. Perhaps this is because the clinical data we obtain from the patient are "fuzzy", *i.e.* open to considerable observer variation.

Over the last year the Yorkshire Breast Cancer Group has carried out studies in observer variation in recording data about breast lesions, and some simple multivariate analyses have been performed. This paper will briefly outline the results of studies to date, and will concentrate not only upon observer variation problems but on the initial simple and multivariate analysis which has been carried out. This analysis has discriminated (in nearly 200 patients) with a high degree of accuracy between benign and malignant lesions on the basis of six clinical factors and a simple "weighting" scale. Finally, the prospects for the next two or three years in this field will be discussed.

HYPERBARIC OXYGEN VERSUS HYPOXIC CELL RADIOSENSITIZERS

By G. E. Adams

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The rationale behind the use of hypoxic cell radiosensitizers (electron-affinic agents) in radiotherapy is, in principle, the same as that behind treatment in hyperbaric oxygen, namely, the elimination of hypoxic cells thought to be present in some human tumours and believed to be a limiting factor in their radiocurability.

Clinical trials with HBO have shown that benefit can be obtained in some situations, but not in others. Overall, however, the results are less promising than originally anticipated. This could be due to arteriolar constriction resulting in a reduction of blood-flow through the tumour capillaries, although a more likely explanation is that oxygen metabolism in the tumour still prevents *all* the hypoxic cells being sufficiently oxygenated in spite of the increased oxygen content in the blood. If some hypoxic cells fail to reoxygenate, even though their proportion might be small relative to the number initially present, this would seriously limit any therapeutic gain from HBO. These limitations are not present for hypoxic cell sensitization with the electron-affinic drugs. Numerous laboratory studies with solid animal tumours using in particular the 2-nitroimidazole Ro-07-0582 as a sensitizer, have consistently shown very large therapeutic gain factors. This is because the very low rate of metabolism of this sensitizer compared with that of oxygen enables the drug to reach all hypoxic cells. The theoretical and practical implications of this result will be discussed and illustrated with laboratory data.

There is some evidence that HBO can lead to a small increase in well-oxygenated normal tissue response. This will not occur with chemical sensitizers unless the tissue concerned contains a significant proportion of naturally-occurring hypoxic cells. The reason for this additional advantage will be discussed.

A CLINICAL APPRAISAL OF HYPERBARIC OXYGEN IN HEAD AND NECK CANCER

By G. H. Berry

Cookridge Hospital, Leeds

The value of hyperbaric oxygen in the radiotherapeutic management of cancer still remains contraversial after 20 years. Despite this, in the radiotherapeutic management of head and neck cancer it appears to have some value. The evidence being presented to support this statement comes from the results of prospective clinical trials carried out in Cardiff and Leeds.

The Leeds trial was commenced after the Cardiff trial and designed to permit the two sets of results being combined if necessary. To achieve this the same criteria for patient selection were used. However, the radiation programme for the two studies differed. The Cardiff study (first trial) gave identical doses in air and HBO whereas the Leeds study gave different doses. For the Leeds study the air dose/fractionation/time was that normally given by the referring consultant and the HBO dose was a reduced dose based on treatment volume and ten fractions given three times weekly. For the oral and nasal groups this corresponded to an N.S.D. of 1900 Ret and for the Larynx-Pharynx groups 1700 Ret.

Randomization was done by the MRC. All patients had bilateral myringotomies before treatment. Treatment was given at a pressure of three atmospheres of oxygen. Radiation was delivered from a 6MeV linear accelerator through a beam direction shell.

A total of 24 patients were studied, randomized as 13 for air and 11 for HBO. One of the latter was excluded leaving ten for assessment. To assist evaluation of the results patients were separated according to the site treated, node involvement and age. Treatment reactions were compared for the two groups at monthly intervals.

Survival and tumour response rates for HBO showed a significant improvement compared with patients treated in air. The results compare favourably with those reported from Cardiff and will be presented. The primary purpose of the Leeds study was to compare morbidity for the two series. Our results reveal no increased incidence of morbidity.

A CLINICAL APPRAISAL OF HYPERBARIC OXYGEN IN CERVIX CANCER

By A. J. Ward, B. Dixon and B. Stubbs

Cookridge Hospital, Leeds

A controlled prospective study has been carried out on 82 patients as collaborative work sponsored by the MRC Hyperbaric Oxygen Working Party to evaluate the role of hyperbaric oxygen in radiotherapy for carcinoma of the cervix. Identical treatment was prescribed with the external beam therapy given either in air or in HBO and the intracavitary component on the cathetron unit.

The patients studied had squamous cell carcinoma of the cervix and were clinically staged 2B (19) and 3 (63). Data obtained from a continuing follow-up suggest a slightly improved survival for those in Stage 3 treated in HBO but a slightly worse outlook for those in stage 2B so treated. There was, however, no significant difference ($p > 0.05$) in survival between the two groups at any time following treatment. Actuarial survival curves obtained suggest a four year survival of approximately 50% overall.

An actuarial analysis also showed that at four years approximately 70% of all cases and 65% of Stage 3 cases would have been tumour free in the treated volume, there being no statistical difference between the local responses of those treated in air or in HBO. An analysis of the rate of clearance of tumour also showed no difference between the two groups.

Metastases were reported in nine patients but were equally prevalent in the two groups. The only clinically significant late morbidity was damage to the small bowel but there was no obvious difference between the two groups.

It appears that there is no significant difference in terms of survival, local clearance of tumour, recurrence, metastasis or morbidity between patients treated in air or in HBO. In this centre, for disease at this site and by this method of treatment, bearing in mind the difficulties of treatment in HBO, it is not considered that treatment in HBO is justified. These results are reviewed in the context of those reported from other centres.

HYPOXIC CELL SENSITIZERS IN CLINICAL RADIOTHERAPY

By S. Dische

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Hypoxic cell sensitizers were introduced into clinical radiotherapy in 1973 when metronidazole (Flagyl) was shown in laboratory study to be an effective drug. A year later another nitroimidazole, the Roche experimental drug Ro–07–0582, was shown to be a more effective agent. With metronidazole each dose must be some 40 times greater than that given in the control of trichomonas. Nausea and vomiting is troublesome but no other immediate side effects have been reported. Dr. Urtasun has established a régime using treatments three times a week over a period of three weeks and has now reported upon a controlled trial in the treatment of gliomas. A significant improvement in survival has been shown and this can be attributed to the effect of the radiosensitizer.

The Roche drug Ro–07–0582 proved, in laboratory study, to be several times more effective than metronidazole. It is, however, a new drug requiring careful toxicological study. A successful trial of single doses in normal volunteers was followed by its administration in single doses to patients. Tolerance was fairly good though nausea and vomiting occurred with the higher doses. By irradiating skin made temporarily hypoxic, the drug was shown to be an effective sensitizer of hypoxic cells in man. In three patients with multiple deposits of tumour, evidence of increased tumour response was demonstrated in those nodules irradiated when Ro–07–0582 was given.

Encouraged by these findings we have proceeded to a multiple dose study. Although there have been no gastrointestinal symptoms and satisfactory plasma levels have been obtained after each dose, the drug has proved to be neurotoxic, producing convulsions and peripheral neuropathy. The dose of Ro–07–0582 which may be used in clinical work must be limited.

New knowledge has accumulated concerning the action of Ro–07–0582 as a radiosensitizer and we now have data as to the tumour concentrations which may be attained in man. It is apparent that there is considerable clinical application possible within this dose range and a chance of a real benefit in clinical radiotherapy using the drug.

THE SEARCH FOR OXYGEN INDEPENDENCE (NEUTRONS, PI MESONS ETC.)

By R. E. Ellis

Department of Medical Physics, Leeds University

The philosopher's stone of much radiobiological research has been to devise a form of radiation treatment which would provide a selective radiation which (i) reacts uniformly with all the neoplastic cells irrespective of their oxygen status and of whether the cells are in the main tumour or are invading through normal tissues. In a fractionated régime the ultimate aim would be to have a situation where no recovery takes place for these neoplastic cells; (ii) at the same time there should be minimal dose and damage to the normal cells and connective tissues within the radiation fields, and these normal cells and tissues should show maximum recovery in the selected fractionated treatment régime.

The progress towards such a goal has been to investigate the radiations which provide higher linear energy transfer (LET) particles in their interaction with tissues: such as neutrons which give protons and recoil nuclei, negative π mesons which give protons and α particles and other heavier nuclei, or the direct use of accelerated heavy ions. The study of sensitizers administered simultaneously with these radiations is also making considerable progress.

The oxygen enhancement ratio (OER) for neutrons of 6 to 17 MeV is about 1.7 and may vary with depth in the range 1.5 to 2.0. Recent information would suggest that as the neutron energy is increased to 60 MeV the OER may reduce to 1.2. The pion beam data indicates that for 70 MeV pions the OER in the peak region is 1.7 and in the plateau region 2.1. There is therefore a case for experimenting with higher energy neutrons and perhaps little to be gained as far as OER is concerned in changing from neutrons to pions. However, this is not all of the story. The gain using pions would be in the distribution which would allow normal tissues to be spared considerably more than with neutrons, *e.g.* in a three-field pion beam the normal tissues would only get 10 to 20% of the peak region. This may be an important factor as has been shown by Allt in Toronto with his comparison of the ten-year survival of patients with cancer of the cervix stage III where a 31% survival is reported on the Betatron and 18% on the ^{60}Co unit, the principal difference being in the dose to the normal tissues.

The main difficulty with heavy ion beams is the very narrow Bragg peak which would necessitate scans both across the beam and in energy to get the maximum in depth and in this way much of the peak to plateau advantage will be lost. The advantage however for ions of carbon and heavier elements is that there is no variation in sensitivity during the cell cycle. This may be an important factor as the variation in sensitivity for X rays is 2.5 during the cell cycle.

Research in the future must therefore concentrate on these unknown factors together with studies of the effect of mixture of high LET first and low LET to follow and the use of radiations and sensitizers together.

A CLINICAL APPRAISAL OF NEUTRON THERAPY

By Mary Catterall

MRC Cyclotron Unit, Hammersmith Hosptial, London

All machines treating patients with fast neutrons are at significant disadvantages compared with megavoltage sources. The 7.5 MeV neutrons from the MRC cyclotron at Hammersmith Hospital produce isodoses which are only equal to 250 kV X rays with rounding of the ends and a penumbra; moreover the beam is fixed in the horizontal position. Other neutron sources in the world are remote from a hospital and available at restricted times only. Despite these disadvantages, comparisons are being made with treatments from linear accelerators and cobalt machines by controlled clinical trials.

The first of these has just been completed at Hammersmith Hospital. Patients with advanced tumour of the head and neck (T_3 or T_4, with or without nodes) were randomized to treatment with neutrons or photons. There was a statistically highly significant advantage to the neutron treated patients in terms of complete regression of tumours and incidence of recurrence. Other comparisons between two pimary tumours in the same patient treated by the two methods have shown recurrences in the photon treated patients but not in the neutron treated patients. Comparisons are also being made of effects on normal structures.

Clinical impressions, not yet tested by controlled clinical trials, are that neutrons are more effective in the treatment of soft tissue sarcoma, adenocarcinoma and glands involved with melanoma.

The cost of neutron therapy is difficult to assess, but at Hammersmith the cyclotron also produces short-lived isotopes which are being increasingly demanded by neurologists, cardiologists, and chest physicians, and in performing activation analyses, useful for endocrine disorders and possibly for other research. Radiobiology orientated to cancer research is another important part of the cyclotron programme.

LYMPHOCYTE CHROMOSOMES, BANDING AND IRRADIATION

By Gillian Kitchingman

Department of Radiotherapy, Leeds University

Human venous blood has been irradiated *in vitro* with single doses either of γ rays, at high and low dose rates, or 14 MeV neutrons produced by the D–T reaction, which were either given continuously at approximately 10 rad/min or in pulses lasting 15 microseconds at a rate of two per second, leading to a cumulative rate of about 0.5 rad/min. Lymphocyte metaphase spreads were examined at their first division in tissue culture, and the number of gross chromosomal aberrations induced by the two types of radiation were compared. The γ-ray data could be defined by an equation indicating that a fraction of the aberrations increased linearly with dose, and the rest increased proportionally to the square of the dose. The relative sizes of the two components varied according to the dose rate. The dose response curves for 14 MeV neutrons were linear throughout, so their RBE increased with decreasing dose. For neutrons given in pulses, the RBE in the dose range 5 to 75 rad was between seven and four. For neutrons given continuously over the same range of doses, the RBE values were approximately half those of pulsed neutrons.

Staining chromosomes to produce G bands shows radiation-induced exchanges and breaks not recognizable by conventional staining techniques. Band position along chromosomes was measured directly, using microdensitometry. Because of variability of band position along normal chromosomes, small radiation induced changes could not be detected, whilst gross changes in banding pattern could be detected by simple examination of the metaphase spread. However, the microdensitometric method does allow the position of chromosomal breaks to be established, without recourse to photography and karyotyping.

An alternative method under investigation utilizes a technique to demonstrate exchanges between sister chromatids which have been found to be significantly increased by irradiation.

TUMOUR PLOIDY AND PROLIFERATION STATE IN RELATION TO RADIOTHERAPEUTIC RESPONSE

By B. Dixon

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The initial clinical response of a tumour to radiotherapy depends not only upon total dose, fractionation, overall time, etc., but may also depend upon the kinetic status and DNA content (ploidy) of the tumour cells and changes brought about during the course of treatment. To determine the relative importance of the kinetic status and ploidy of cervical tumours in determining their clinical response, pre-treatment biopsies from patients undergoing intracavitary high dose-rate ^{60}Co cathetron or low dose-rate ^{137}Cs intracavitary irradiation are being studied by means of *in vitro* labelling with ^{3}H–TdR and ploidy measurements of Feulgen stained preparations of tumour cells.

^{3}H–TdR labelling indices (LI) have been obtained ranging from 1.8% to 27.8%. No correlation is observed between mean LI's and the histological type of tumour or its degree of differentiation. Comparison with previously reported data indicate that with increasing clinical stage in cervical carcinoma a considerable lengthening of the potential doubling time of tumour cells—from less than one to eight days—occurs. Vaginal spread of tumour is directly related to the degree of parametrial involvement and the mean time taken for the vaginal component of the tumour to resolve following radiotherapy is related to initial spread and pre-treatment LI. Up to one year following radiotherapy the incidence of local recurrence, or metastatic disease, is unrelated to pre-treatment LI.

Microdensitometric analyses indicate that the ploidy status of cervical tumours varies from diploid to aneuploid. For those with bimodal DNA distributions estimation by probit transformation of the proportion of cells synthesising DNA correlates with that measured by ^{3}H–TdR autoradiography. Measurement of sequential biopsies from patients indicates that the technique may in qualitative terms be useful in assessing proliferative status of tumour cells during a course of treatment.

COMBINATION CHEMO- AND RADIOTHERAPY OF A TRANSPLANTABLE, METASTASIZING TUMOUR

By J. V. Moore

Paterson Laboratories, Christie Hospital, Manchester

The use of cytotoxic drugs as adjuvants to radiotherapy has become increasingly common. The usual rationales for the use of such adjuvants are: (1) an increased effect on a primary tumour, either through the independent actions of the two modalities or through their interaction; and (2) the cytotoxicity of the drugs on any occult distant metastases.

In these contexts, the response to γ-irradiation alone and to irradiation plus cyclophosphamide (CP) was examined for a rat mammary carcinoma. Tumour response was measured in terms of delay in its overall growth after CP and/or irradiation, and of changes in its cellular kinetics over several days after a high dose of CP. At a time after drug when DNA synthesis and mitotic activity were least, the response of the tumour to irradiation suggested that the fraction of hypoxic cells was higher than before treatment. Thus, while the combination CP–γ was usually additive in effect, at this interval (four days) the effect was less than additive. Further, the adjuvant use of high doses of CP apparently enhanced the rate and extent of disseminated disease.

STUDIES OF BONE STRUCTURE AND DOSIMETRY OF BONE-SEEKING RADIONUCLIDES. SOME RESULTS AND IMPLICATIONS

By F. W. Spiers

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Measurements of the microscopic structure of human and animal bone have been made in order to determine the dose to the tissues of bone from radionuclides incorporated in the bone matrix or on bone surfaces. The measurements, however, are relevant to a wider field of bone studies than the purely dosimetric and some of these other aspects will be included in this paper.

In order to determine the dose from β or α particles crossing an irregular structure like trabecular bone, the interpenetrating arrangement of bone and soft tissue is quantified in a special way by measuring two frequency distributions of path lengths (1) through the trabecular and (2) through the marrow spaces. The distributions of path lengths through trabecular bone are measured automatically by means of a scanning microscope viewing low voltage radiographs of very thin sections cut from metal-embedded specimens. A modified method is used for cortical bone.

In brief outline, the structure of human trabecular bone is characterized by path lengths that average about 200 μm through the trabeculae and some 1000 to 1500 μm through the marrow spaces, the values differing for different bones. In animal bone the trabecular path lengths are similar to those in human bone but the marrow path lengths are very much smaller.

Some results of the dosimetry will be given to illustrate how the dose rate depends on bone structure. In general the dose rates are higher in young than in adult bone and very much greater in animal bone than in man.

Other parameters relevant to bone studies, such as the percentage bone and the surface-to-volume ratio, can be derived from our measurements and examples will be given to show species and age differences. In particular the total endosteal surface area in the trabecular and cortical parts of the six long bones of an adult human subject have been determined. Comparison of these results with records of the frequency of bone sarcoma (both natural and radiogenic tumours) has shown that the probability of tumour occurrence correlates well with trabecular but not with cortical area. It can be deduced that the probability of sarcoma occurrence per unit surface area is about five to six times greater in trabecular than in cortical bone.

THE DYNAMIC ASPECTS OF BONE TUMOURS

By J. M. Fitton

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During the period of growth of the skeleton the position and extent of tumours and cysts in long bones depends on three factors: the site of origin, the expansion of the tumour and the growth of bone from the epiphysis. The site and change of tumours and cysts in bones is important in diagnosis, and in certain cases it may help the surgeon to decide whether or not to undertake exploration and biopsy.

The distinction between change in a lesion due to its expansion and to growth at the epiphysis is difficult to evaluate. It is possible to prepare charts of bones showing growth and then to locate on these bone tumours and cysts. Such charts showing the growth of certain long bones and the behaviour of certain lesions will be illustrated. From these it is possible to formulate ideas about the time and place of origin of certain lesions.

THE PLACE OF RADIOTHERAPY FOR BONE TUMOURS

By L. A. Firth

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A review of the literature reveals the inadequacy of our knowledge. A few points emerge.

Recent advances in chemotherapy have reduced the need for radiotherapy in osteosarcoma, but when radiation *is* the primary treatment the lengthened survival demands a good local result. Histological studies suggest that doses of about 10000 rad are required. All the cured patients in Brzaković's series received orthovoltage; this, with the work of Urtasun on cell cultures, merits further attention. Chambers and Mahoney achieved a 73% survival in osteosarcomas of the mandible treated by radium implant and hemimandibulectomy.

A number of dramatic remissions have been recorded following therapy of chondrosarcoma with ^{35}S. Malignant fibrous histiocytoma may be more radiosensitive than has been supposed, and radiotherapy is possibly indicated in inoperable disease. Several recent articles on bone metastases suggest that single exposures are as effective as longer courses, and that small doses are adequate. The nature of the primary is not important. Good palliation can often be obtained with ^{32}P.

Although unfashionable in these days of multicentre trials, brief but detailed case reports are still important in accumulating information on these rare tumours and should be encouraged.

1978, *British Journal of Radiology*, *51*, 154–158

Proceedings of The British Institute of Radiology

The Annual Congress, Scientific Exhibition (April 14–15, 1977)

Fine needle percutaneous cholangiography in biliary atresia, by H. B. Nunnerley, I. P. Wells, E. R. Howard and A. Mowat.
The radiology of slipped femoral capital epiphysis, by T. J. Bloomberg and D. J. Stoker.
The radiologist in the management of massive lower gastro-intestinal bleeding, by J. F. Reidy.
Antegrade intubation barium examination of the small intestine, by D. J. Nolan and N. Pantelidis.
A study of the relationship between eye movements and observer performances in diagnostic radiology, by F. Johnson and B. S. Worthington.
Contrast laryngography, by A. H. Chalmers and A. Mills.
Flow patterns at constrictions, branches and bends, by A. E. Hugh.
Infusion tomography of the gall-bladder, by R. Wilkins and P. Renton.
The radiology of the loin pain haematuria syndrome, by P. B. Guyer.
The use of a wedge filter in the double contrast barium enema, by G. de Lacey, B. Wignall and C. Bridges.
Lymphangiogram pump, by A. Amos and W. F. White.
The arteriographic anatomy of the coronary arteries, by Sally Allwork, D. Hawtin and M. Raphael.
Anatomical aid for the interpretation of EMI scan images, by R. E. Coupland, B. Logan and B. S. Worthington.
Computerized tomographic appearances of the pelvis, by L. Kreel and Brenda Sandin.
Comparison of ultrasound and computerized axial tomography in the diagnosis of pancreatic disease, by H. B. Meire, Janet Husband and L. Kreel.
Normal fetal anatomy as shown by grey scale ultrasound, by A. Paris.
EMI/SHM automated isodose plotter—radiation beam data from both manual and computer control, by G. D. Lambert M. Fitzgerald and D. Doughty.
Application of a radiotherapy simulator for imaging body cross sections, by S. Webb, S. C. Lillicrap, Heather Steere and R. D. Speller.
Iron-52 as a bone marrow scanning agent, by Heather A. Steere, S. C. Lillicrap, H. M. Clink and M. J. Peckham.

FINE NEEDLE PERCUTANEOUS CHOLANGIOGRAPHY IN BILIARY ATRESIA

By H. B. Nunnerley, I. P. Wells, E. R. Howard and A. Mowat

Departments of Diagnostic Radiology and Paediatrics
King's College Hospital

An exhibition was mounted to demonstrate the contribution of fine needle percutaneous cholangiography to the confirmation of the diagnosis and to the assessment of the extent of biliary atresia in infants. The technique involves the introduction of a 23 gauge Okuda needle via the lateral intercostal approach under general anaesthetic. This allows normal biliary ducts to be opacified even in infants. Hepatic and portal venous filling may also be obtained. Cholangiograms demonstrating hypertrophy of hepatic lymphatics imply biliary duct atresia. This was illustrated and a further case of intra-hepatic atresia with normal extra-hepatic ducts was accompanied by a peroperative cholangiogram for confirmation. Clot in the portal vein is a well recognized complication of the disease, and one cholangiogram showed clot in the portal vein with collateral formation.

The surgical technique for the relief of jaundice in biliary atresia involves anastomosis of hypertrophied hepatic lymphatics to a loop of jejunum (Kasai Procedure). A postoperative percutaneous cholangiogram demonstrating flow of contrast via lymphatics into the jejunum was shown. The anatomy had been confirmed during screening by seeing peristalsis in the loop of jejunum.

THE RADIOLOGY OF SLIPPED FEMORAL CAPITAL EPIPHYSIS

By T. J. Bloomberg and D. J. Stoker

Department of Radiology
Royal National Orthopaedic Hospital

This demonstration illustrates the radiographic spectrum of the condition and is based on a study of 114 patients seen at the Royal National Orthopaedic Hospital.

The diagnosis is based on radiographic appearances and the most helpful are detailed.

Although the diagnosis can often be made on a frontal radiograph, in 11% the slip can only be demonstrated on the lateral film.

A variety of conditions associated with slipped femoral capital epiphysis are illustrated.

THE RADIOLOGIST IN THE MANAGEMENT OF MASSIVE LOWER GASTRO-INTESTINAL BLEEDING

By Dr. J. F. Reidy

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Massive lower gastro-intestinal bleeding is an uncommon but potentially dangerous situation. Fortunately, in the majority, bleeding will stop with conservative management. Only occasionally is it severe enough to warrant surgery. Conventional radiology is of little value in localizing the bleeding and, even at laparotomy, finding the bleeding site is usually impossible. Faced with this situation, the surgeon usually has no choice but to remove most of the colon, a major procedure in patients who are often elderly and "at risk". In such cases angiography performed while bleeding is occurring will usually demonstrate the site. Six cases showing bleeding due to a variety of causes were demonstrated. In all patients selective injection into the superior mesenteric artery showed extravasation of contrast medium. The radiologist's role is emphasized: not only can he localize the site of bleeding but he can also stop the haemorrhage by infusing the same catheter with pitressin. If this is successful he may well save the patient from major surgery. Even if the bleeding does not stop or recurs, a limited resection is then possible. This service, both diagnostic and therapeutic, should be well within the range of any general X-ray Department doing angiography.

ANTEGRADE INTUBATION BARIUM EXAMINATION OF THE SMALL INTESTINE

By D. J. Nolan and N. Pantelidis

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The big disadvantage of the follow-through barium examination is that the pyloric sphincter prevents adequate filling of the loops of the small intestine. The action of the pyloric sphincter is overcome by passing a Bilbao-Dotter duodenal tube (Sellink modification) to the ligament of Treitz. Dilute barium (S.G. 1.2—1.3) is then infused at a rate of approximately 100 ml/min and radiographs are obtained of the small intestine well distended with barium. A total of 600 to 1200 ml of barium is infused and the terminal ileum is reached in five to ten minutes. Air or water may be used to obtain double contrast views, where necessary. The technique is similar to that described by Sellink (1976).

Our initial experience indicates that this is a far more accurate method than the follow-through as normal segments of the intestine can be clearly shown and the extent of diseased segments accurately estimated. The time taken for the examination is normally 20 to 30 minutes.

REFERENCE

SELLINK, J. L., 1976, *Radiological Atlas of Common Diseases of the small Bowel* (Leiden, H. E. Stenfert Kroese B.V.).

A STUDY OF THE RELATIONSHIP BETWEEN EYE MOVEMENTS AND OBSERVER PERFORMANCES IN DIAGNOSTIC RADIOLOGY

By F. Johnson and B. S. Worthington

University Hospital and Medical School, Nottingham

Eye movements are an inherent part of inspecting a radiological image. Observers of differing radiological experience searched without time limit a series of chest X-rays, some of which had a single low density coin lesion superimposed on one lung field. The number of fixations to detect the lesions was recorded using an NAC Eye Mark Recorder.

In the case of normal films, measurement was made of the number of fixations to complete a search to the satisfaction of the observer. Histograms of the fixation times and interfixation distances were prepared from the data.

The observers showed a similarity in respect of their modal fixation times and in the distribution of interfixation distances. The less experienced observers showed a tendancy to fixate on sharp edges in the image and to ignore the peripheral lung fields. In general, the more experienced the observer the shorter was his mean fixation time and the smaller was the number of fixations, both to detect a lesion and to complete a search of the film.

CONTRAST LARYNGOGRAPHY

By A. H. Chalmers and A. Mills

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The exhibit discussed the use of contrast laryngography, described the technique and showed examples of lesions affecting the various parts of the larynx.

Contrast laryngography provides better anatomical detail than tomography, and by taking films during inspiration, phonation, modified Valsalva and Valsalva manoeuvres normal mobility of the cords and related structures can be shown. The subglottic area is well shown and the larynx can also be demonstrated in cases when direct laryngoscopy is impossible due to bulky proximal tumours.

The patient is premedicated with two Actifed tablets to reduce secretions and then the larynx is anaesthetized by trickling Lignocaine 4% over the back of the tongue, followed by Oily Dionosil. P. A. and lateral films are taken during each breathing manoeuvre.

Tumours are diagnosed by showing an irregular mass and the extent determined by showing invasion or immobility of local structures. The anterior commissure is readily assessed as well as the rest of the larynx. The examination takes about 20 minutes on a screening unit and although more unpleasant than tomography for the patient, does provide more information.

FLOW PATTERNS AT CONSTRICTIONS, BRANCHES AND BENDS

By A. E. Hugh

North Staffordshire Hospital Centre

In a model constucted of 4 in. half-round plastic guttering, flow patterns are demonstrated using fine aluminium powder sprinkled on the surface of the circulating water impelled by a paddle-wheel.

At constrictions, both upstream and downstream stasis is seen, in the angle between the vessel wall and the constriction. After prolonged circulation focal deposits of powder form consistantly in certain areas on either side of the stenosis, which could well be of significance in physiological situations. However, the most striking feature shown in both short and long constrictions is retrograde flow of particles in the boundary layer, to the low-pressure area at the mouth of the constriction. This occurs despite very rapid flow in the main channel of the constriction, and is suggested to be an important mechanism causing narrowed vessels to block off completely.

At branches, the uneven velocity of fluid particles is well shown. High-velocity particles are seen to lift off the vessel wall, leaving areas of stasis in two consistant areas—in the main channel, opposite the branch mouth, and within the branch mouth, on its outer (or upstream) wall. Depending on the amount of flow this stasis can extend along a considerable length of channel.

At bends, spiral "in depth" currents are a prominent feature, together with areas of stasis at certain areas on the vessel wall.

Zones of stasis and retrograde flow are thought to be of great importance in the arterial system, and their place in a two-cycle theory of atherogenesis is shown in an accompanying diagram.

INFUSION TOMOGRAPHY OF THE GALL-BLADDER

By R. Wilkins and P. Renton

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Watford Road, Harrow, Middlesex

This is a technique for the radiological diagnosis of acute cholecystitis. It relies upon the principle of total body opacification with water soluble contrast media during which an inflamed organ becomes more radio-dense than the surrounding tissues. No preparation is needed for this technique and the entire procedure takes approximately 40 minutes. Infusion cholecystography can be undertaken even in the prescence of jaundice of vomiting.

An initial scout radiograph of the right upper quadrant is taken, following which 300 ml of Methylglucamine Diatriazoate (30%) is infused intravenously over a 15–20 minute period. Immediately after the infusion, A. P. or P. A. tomograph cuts of the gall-bladder region are taken. A negative examination in which there is no radiological evidence of acute cholecystitis is made when there is no opacification of the gall-bladder wall. A positive examination is represented by a ring shadow in the right upper quadrant representing the inflamed gall-bladder wall. The gall-bladder lumen is seen as an unopacified lucent centre. In some instances calculi may be seen within this.

This technique has been used effectively in our department for a short time and our results have been in keeping with those described by Love (1976) who found a 90% accuracy rate in the diagnosis of acute cholecystitis, there being only one false negative examination out of a total of 27 patients.

This radiological technique is particularly recommended in those institutions in which cholecystectomy is performed during the acute phase.

REFERENCE

Love, L., 1976. Infusion tomography of the gall-bladder. *Seminars in Roentgenology*, *11*, 181–184.

THE RADIOLOGY OF THE LOIN PAIN HAEMATURIA SYNDROME

By P. B. Guyer

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Examples from angiograms from 13 patients were demonstrated. They were all young females, mostly aged 18 to 25 years, with recurrent loin pain which is normally bilateral, and accompanied by haematuria, which may be microscopic only. A prominent feature of the case histories has been the tendency to psychological disorders such as hysteria, dermatitis artefacta, and attempted suicide. Many, but not all, of the patients have at some stage received oral contraceptives. Physical examination is normal except for loin tenderness during attacks. Tests of renal function are also normal.

Excretion urography is normal in this condition. Angiography was bilaterally abnormal in 12 of the 13 patients, and abnormal in one side only in the 13th patient. The main abnormality is in the nephrogram where there are widespread cortical defects with loss of differentiation between the cortex and medulla; these changes may affect part or the whole of either kidney. In addition to this many patients show arterial irregularities and tortuosity, and most patients show some evidence of vascular stasis with prolonged arterial filling in the area of the abnormal nephogram. A few patients show actual arterial occlusion, with resulting visible renal infarction, as shown by larger areas of renal ischaemia.

THE USE OF A WEDGE FILTER IN THE DOUBLE CONTRAST BARIUM ENEMA

By G. de Lacey, B. Wignall and C. Bridges

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St. Georges' Hospital, London

On lateral decubitus views there is increased absorption of the X-ray beam by soft tissues on the dependent side, and in some obese patients this may cause unilateral under-exposure or over-exposure. This uneven film blackening is readily overcome by using a wedge filter which slides temporarily on to the tube head. The filter is constructed of Dural measuring 110 mm × 65 mm and tapering from 20 mm to zero and mounted on a Tufnol base. Tufnol is a strong resin impregnated linen cloth and is cut to fit the filter mounting on the tube head. The kV is increased by five above that which would otherwise be required to provide adequate penetration of the elevated side. This allows optimal film blackening of the dependent side, but the filter prevents excess blackening of the opposite and elevated side. Photographs of the wedge filter, and radiographs of decubitus views with and without the filter were included in the exhibit.

LYMPHANGIOGRAM PUMP

By A. Amos and W. F. White

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The lymphangiogram pump demonstrated at the Scientific Exhibition of the B.I.R. Congress 1977 resulted from an idea, in discussion with Dr. Hugh Saxton, to produce a method of injecting lipiodol ultra fluid other than by using an electric pump. The basic motive force is compressed carbon dioxide which comes in a convenient form in "sparklet" cylinders. The gas is released into a large chamber and through this via pressure controls to cylinders which compress standard syringes. In this way a constant pressure can be applied to the syringe plungers.

In a large regional centre where lymphangiograms have been carried out in a number of different departments, both radiological and radiotherapy, together with medical and surgical departments, it was found that there was considerable variation in the type of electrical sockets and the need for a variety of electrical connections. The method was developed in order to overcome this problem so that the pump could be entirely portable and free of any other motive force.

By varying the pressure applied to the syringes the flow rate through a lymphangiogram injection set can be varied and calibrated, the pressure flow dynamics being an individual parameter for each type of lymphangiogram set. The lymphangiogram pump is simple in construction and operation and affords the possibility of carrying out the procedure under variable conditions with complete electrical safety.

THE ARTERIOGRAPHIC ANATOMY OF THE CORONARY ARTERIES

By Sally Allwork, D. Hawtin and M. Raphael

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Hammersmith Hospital, London, W.12

The beginner in coronary arteriography has considerable difficulty in understanding coronary anatomy in terms of three dimensions. To aid in understanding we have prepared a series of casts of the coronary arteries of the human heart, and photographed these in projections similar to those used in coronary arteriography. The casts have been matched with comparable coronary arteriograms.

ANATOMICAL AID FOR THE INTERPRETATION OF EMI SCAN IMAGES

By R. E. Coupland, B. Logan and B. S. Worthington

Department of Human Morphology
University Hospital and Medical School, Nottingham

A technique for the preparation and mounting of head sections has been developed for the purpose of facilitating the interpretation of EMI scan head images.

A casting box was constructed with a wooden base and polished Perspex sides. The bottoms of the sides were fitted into slots on the base and the tops were held together with specially constructed clips.

A deep frozen embalmed head was placed on its side on the centre of the base supported by blocks of plasticine with the median sagittal plane parallel to the base board and the orbito-meatal line parallel to one side of the box and at right angles to the adjacent side. The sides of the box were then put in place and clipped into position.

Fine sand was then poured into the box to a level ensuring the visibility of the median sagittal plane of the head. Plaster of Paris was poured in until it covered the head to a depth of about 2 cm.

After further deep freezing, sections were made with a band-saw either in or parallel to the orbito-meatal line at intervals of 1 cm and placed serially into a fluid prepared according to the Wentworth technique and finally mounted in Perspex containers.

The specimens are of particular value in the interpretation of EMI scan images. Where the plane of section passes through or below the third ventricle, it materially assists in the identification of structures related to the tentorium cerebelli and lying in or adjacent to the posterior cranial fossa.

COMPUTERIZED TOMOGRAPHIC APPEARANCES OF THE PELVIS

By L. Kreel and Brenda Sandin

Division of Radiology Clinical Research Centre
Northwick Park Hospital, Harrow

An important feature of examinations by CT is the ability to show soft tissues. The demonstration of soft tissue abnormalities in the pelvis is often of great importance in diagnosis for decisions which directly affect management. In order to do this, an appreciation of normal anatomy is required.

The conditions which need to be defined include tumours of the cervix, uterus and ovaries, extension of these tumours to lymph nodes, the visualization of tumours in the bladder, and diffuse infiltration which may affect pelvic soft tissues.

CT scanning also produces high definition pictures of bone, so that small sclerotic and lytic deposits can be defined.

COMPARISON OF ULTRASOUND AND COMPUTERIZED AXIAL TOMOGRAPHY IN THE DIAGNOSIS OF PANCREATIC DISEASE

By H. B. Meire, Janet Husband and L. Kreele

Department of Radiology
Clinical Research Centre and Northwick Park Hospital
Harrow, Middlesex

The exhibit includes examples of the normal pancreatic appearances and anatomy as demonstrated by computerized tomography and ultrasound. The importance of identifying the structures related to the pancreas is emphasized, especially with respect to the interpretation of the ultrasound images. The typical appearances of acute pancreatitis, chronic pancreatitis and the sequelae of pancreatic inflammation, as demonstrated by both techniques, is shown. Examples of pancreatic carcinoma and the criteria for its diagnosis are also included. The majority of comparitive images were taken by both techniques on the same patients at the same anatomical levels and the ability of each technique to visualize both the pancreas and other structures at that level can also be seen.

A preliminary analysis of our early results is included. This shows that in the first 50 patients ultrasound had a small but significant failure rate owing to bowel gas, but in those patients in whom adequate examinations were obtained the diagnostic accuracy for both techniques is about 85%.

NORMAL FETAL ANATOMY AS SHOWN BY GREY SCALE ULTRASOUND

By Miss A. Paris

Northwick Park Hospital and Clinical Research Centre
Watford Road, Harrow, Middlesex

This exhibit demonstrates the ultrasonic appearance of the fetus at different stages of gestation.

The size of the gestation sac at the sixth week after the last menstrual period is shown together with a time position scan of the fetal heart movements.

Crown rump lengths of the fetus are recorded in the seventh, eighth, tenth and twelfth weeks of gestation. Some of the anatomical structures shown on longitudinal scans are demonstrated in both a mid-term fetus and in one over 30 weeks.

The fetal spine is illustrated at 16 weeks and, in cross-section, anatomy of the lower chest and upper abdomen in a fetus under 20 weeks.

A section of the exhibit displays anatomical structures which can be demonstrated in fetuses over 26 weeks when scanned in cross-section. Structures include the heart and intra-ventricular septum, the aortic arch and the whole length of the abdominal aorta; the kidneys and renal pelyces and urine-filled bladder, the distended stomach, umbilical vein and fetal liver.

The prints used for the exhibit were selected from both 70 mm negatives taken with a Shackman Super Seven camera attached to a 5 in. TV monitor and from 35 mm negatives exposed to an 11 in. TV monitor.

EMI/SHM AUTOMATIC ISODOSE PLOTTER—RADIATION BEAM DATA FROM BOTH MANUAL AND COMPUTER CONTROL

By G. D. Lambert, M. Fitzgerald and D. Doughty

Department of Radiation Physics
St. Bartholomew's Hospital
London EC1A 7BE

This exhibit was arranged to convey the scope and performance of the EMI/SHM Automatic Isodose Plotter which was recently borrowed from the DHSS.

The equipment was used under computer control—for beam data acquisition for the Rad 8 treatment planning system, and under manual control—for depth dose, profile and isodose plotting. A description of the equipment was followed by a display and comparison of results obtained using both modes of control.

Manual control proved to be a straightforward, rapid and accurate method of depth dose and profile plotting. Isodose plotting was found to be only semi-automatic in that the plotting velocity had to be controlled continually to minimize fluctuations in the plots. One radiation field took typically 20 minutes to complete. The computer controlled mode was very efficient, a complete set of beam data for a treatment unit (say 80 fields) taking only two days to measure including set up and trials.

Comparisons showed that isodoses drawn by the Rad 8 treatment planning program were in close agreement with those produced by the plotter in the manual control mode, particularly after smoothing the computer data. Differences were thought to be due to inadequacies of the computer algorithm rather than incorrect data values and could be reduced by slight adjustment of the beam profile values.

APPLICATION OF A RADIOTHERAPY SIMULATOR FOR IMAGING BODY CROSS SECTIONS

By S. Webb, S. C. Lillicrap, Heather Steere

Physics Department,
Institute of Cancer Research and Royal Marsden Hospital
Sutton, Surrey

and R. D. Speller

The Middlesex Hospital Medical School
Cleveland Street, London, W1

A map of cross sectional tissue structure and associated linear attenuation coefficient within the body contour has been obtained by the technique of reconstruction from X-ray transmission projections recorded with a radiotherapy simulator. The technique allows reconstruction tomography with its applications for treatment planning to be available to departments of radiotherapy possessing conventional radiotherapy planning equipment.

We present a grey scale reconstruction picture showing the distribution of tissue within a two-dimensional slice of a chest phantom. The experimental technique for obtaining such images is outlined, together with the relevant theoretical algorithms, namely the convolution and back projection mathematics incorporated within the SNARK 75 package.

The success of the reconstruction is discussed in terms of spatial and density resolution and the associated sampling intervals.

The advantages of setting up a simple locally built reconstruction facility are outlined.

IRON-52 AS A BONE SCANNING MARROW AGENT

By Heather A. Steere, S. C. Lillicrap, H. M. Clink and M. J. Peckham

The Royal Marsden Hospital and
Institute of Cancer Research
Downs Road, Sutton, Surrey SM2 5PT

Iron-52 has been in routine use as a bone marrow imaging agent for over two years. Whole-body digital scans are carried out 20 hours after the intravenous administration of μCi Fe-52 as the citrate.

Initial studies consisted of finding the distribution of iron-52 in normal and various groups of abnormal subjects and hence calculating the radiation dosimetry associated with the test. Subsequently, specific groups of patients have been examined with a view to (a) examining quantitatively the extent of depression, followed by regeneration and redistribution of bone marrow function after large field radiotherapy in patients with lymphoma, and (b) establishing the extent of extramedullary haemopoiesis in pancytopenic patients and hence deciding on the advisability of splenectomy in such patients.

Summarized results and conclusions from all studies were presented.

Book review

Percutaneous Transluminal Angioplasty. By G. J. van Andel, pp. 166, illus., 1976 (Excerpta Medica, Amsterdam-Oxford, American Elsevier Publishing Co., Inc., New York), $19.25. (Dfl.50.00).

The first few chapters in this book, describing the anatomy of the arteries of the pelvis and legs, the pathology and clinical signs of peripheral atherosclerosis are not particularly interesting but as the text progresses the interest quickens rapidly. There is an excellent chapter, very well documented, discussing the therapeutic options in chronic arterial occlusive disease and this is followed by a detailed description of transluminal angioplasty, starting with the original simple Dotter procedure and proceeding to all the refinements in technique which have been added subsequently, including recanalization of the iliac arteries. The indications and contra-indications for the method are dealt with exhaustively and the complications are not ignored.

The nub of the work, however, lies in the last two chapters in which, with commendable honesty, the author gives the results in his personal series and evaluates the various procedures. The results are in much too detailed form to be summarized here but the main conclusions, as would be expected, are that stenoses are easier to deal with than occlusions and that the shorter the occlusion, the easier it is to treat.

The text is clear and well written. This book is essential for anyone wanting to evaluate the Dotter procedure.

J. D. Dow.

Obituary

George Simon, M.D., M.B., B.Chir., D.M.R.E., F.R.C.P., M.R.C.S., L.R.C.P,. F.R.C.R.

Dr. George Simon died on September 30, 1977 leaving a vacant place in the teaching of radiology far, far, larger than his modesty would acknowledge. The students, not only radiological, to whom he gave tutorials throughout his career at St Bartholomew's and the Brompton Hospital, and for ten years thereafter at Hammersmith, King's, the National Heart, Northwick Park and University College Hospital, have lost an irreplaceable friend. Each of us who had the privilege and fun of knowing him began with gratitude for his interest; we were stimulated by his intelligence and amused both by his sudden wit and his unique and unselfconscious ways; we soon loved him because he concerned himself for us all the time.

He is irreplaceable, but of such vivid and strong presence that everyone who knew him will always be able to recall his smile, his argumentative challenge and his voice. There are many George Simon stories. One that may be remembered here was his ambition for the future, privately expressed a year or two before he retired. "Going to be a butler", he said. "Very useful people", and with that in mind he went on serving and guiding the young until his death.

To George Simon's teaching, which included the authorship of a number of very useful books running to several editions—*Surface and Radiological Anatomy*, *X-ray Diagnosis*, *Principles of Chest X-ray Diagnosis*, *Principles of Bone X-ray Diagnosis*, must be added his achievements in original scientific work, especially his many publications on radiology of the chest. His original work was so good because it was always based upon the closest attention to pathological changes found in the specimen and was par excellence cooperative with physican, surgeon and pathologist. Perhaps, indeed, his greatest contribution of all to British radiology lay in the way he showed us how to work with clinicians rather than in isolation.

He first became Clinical Assistant to the X-ray Department at Bart's in 1927, Chief Assistant in 1928 and half-time Assistant Radiologist (Consultant) in 1946. During the late 1940s British radiology suffered in many teaching hospitals from a lack of respect based, by and large, upon failure to understand the clinical background that led to its daily work. George knew that what was wrong was a lack of communication. For a year or more he lambasted the physicians and surgeons with the phrase that then characterized for him the whole unsatisfactory situation. "No clinical co-operation!" It was dictated and sent off as a report.

Then he changed his tactics, taking the battle into the wards away from the X-ray Department itself, realizing that only by example could he make radiology more relevant by discussing face to face the indications for an X-ray examination and the interpretation of the findings. From then until his retirement in 1967 he spent part of every day with a succession of clinical firms and was to be seen, a large bundle of X-ray envelopes under his arm, hurrying to his scheduled meetings, always bustling, very rarely late. His comments and questions at these meetings were not only very helpful in the management of the patient concerned, they often also defined where we were ignorant and thus led to clinically useful research.

George Simon had an international reputation and travelled extensively in the United States, lecturing and listening. He was a very great and famous man, and to this must be added as a kind of crowning glory that every enquiry "Do you know George Simon?" of whomsoever it was made and in whatever country, when answered, as always, "Yes", provoked an accompanying smile.

We, his colleagues, knowing the unselfishness of his friendship can imagine how his wife and children must miss him, but they must be very proud of him too.

G. H. DU BOULAY.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *B.I.R. BULLETIN* which is distributed quarterly to all members.

THE THEORY AND PRACTICE OF DATA DISPLAY

A joint meeting of I.E.R.E./I.E.E./H.P.A./B.I.R./E.T.A., will be held on February 13, 1978 at The Royal Institution, Albermarle Street, London, W.1.

Information and registration from The Meetings Officer, I.E.R.E., 99 Gower Street, London WC1E 62Z.

RADIOBIOLOGY MEETINGS

The following meetings are scheduled:

"Work-in-progress", February 17, 1978;

"Recent advances in hyperthermia research", May 18, 1978.

Further information from the General Secretary, B.I.R. (01–935 6237).

CARCINOMA OF THE BLADDER

A joint meeting of the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists, will be held on February 17, 1978 at the R.S.M., London, W.1.

Details from the R.S.M., 1 Wimpole Street, London, W.1.

COMPARISON OF DIAGNOSTIC TECHNIQUES FOR THE CHEST AND MEDIASTINUM

An evening meeting will be held on March 16, 1978 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Details and registration from the General Secretary.

B.I.R. ANNUAL CONGRESS JOINT MEETING AND SCIENTIFIC EXHIBITION 1978

The Annual Congress will include a joint meeting with the Royal College of Radiologists, the Royal Society of Medicine (Section of Radiology) and the Netherlands Society of Radiology and will be held at the R.I.B.A., London, W.1. on April 13–14, 1978. Enquiries concerning the Scientific Exhibition should be addressed to Dr. J. Pemberton, St. Thomas's Hospital, London, S.E.1 (01–928 9292). All other details from the General Secretary.

The "SILVANUS THOMPSON MEMORIAL LECTURE" will be delivered at this congress by Sir John Hill, Chairman U.K.A.E.A.

SECOND CONGRESS OF THE EUROPEAN SOCIETY OF NUCLEAR MEDICINE

The Institute and other UK members of the European Society of Nuclear Medicine will be hosts to this congress to be held in London, April 17–18, 1978. The meeting will include a commercial exhibition, scientific demonstrations and technologists sessions.

Further information from General Secretary B.I.R.

B.I.R. CONVERSAZIONE

Will be held at Northwick Park Hospital, Middlesex on May 17, 1978. Dr. Louis Kreel will arrange demonstrations and give a talk "*Introducing art into radiology*".

Details from the General Secretary.

HIGH DOSE RATE AFTERLOADING GYNAECOLOGICAL IRRADIATION AS AN ADJUVANT TO GYNAECOLOGICAL SURGERY: AN ASSESSMENT OF THE CATHETRON

An evening meeting will be held on May 18, 1978 at The British Institute of Radiology (Reid-Knox Hall), 32 Welbeck Street, London W1M 7PG.

Further details from the General Secretary.

BENIGN BONE DISEASE–ROLE OF RADIOISOTOPE TECHNIQUES

A joint meeting of the British Orthopaedic Association and The British Institute of Radiology, will be held on May 31, 1978 at the Middlesex Hospital Medical School, London. Proffered papers are invited and titles and abstracts should be sent to Dr. P. J. Ell, Department of Nuclear Medicine, Middlesex Hospital Medical School, Mortimer Street, London W1N 8AA by March 1, 1978.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

Corrigendum

Vertebral aspergillosis with preservation of the disc, by M. Rassa. (December 1977).

Dr. Rassa has drawn attention to a misprint in his recent paper. On page 918, first paragraph, column 1, line 10 should read "patient in whom the discs were spared."

We apologize for this error.

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Books received

Receipt of the following books is acknowledged as a courtesy to the sender. These publications have been lodged in the Library of The British Institute of Radiology for the use of members.

Activités Scientifiques et Techniques, 1976. Commissariat à l'Energie Atomique, Paris, France, pp. 238, illust.

Commissariat à l'Energie Atomique–Annual Report, 1976. Paris, France, pp. 110, illust.

Directory of on-going Research in Cancer Epidemiology, 1977. (*IARC Scientific Publications No. 17*). Eds: C. S. Muir, G. Wagner. Technical Ed. for IARC, W. Davis. pp. xii + 599 (Switzerland, World Health Organization), $10.00 Sw.Fr.25.00.

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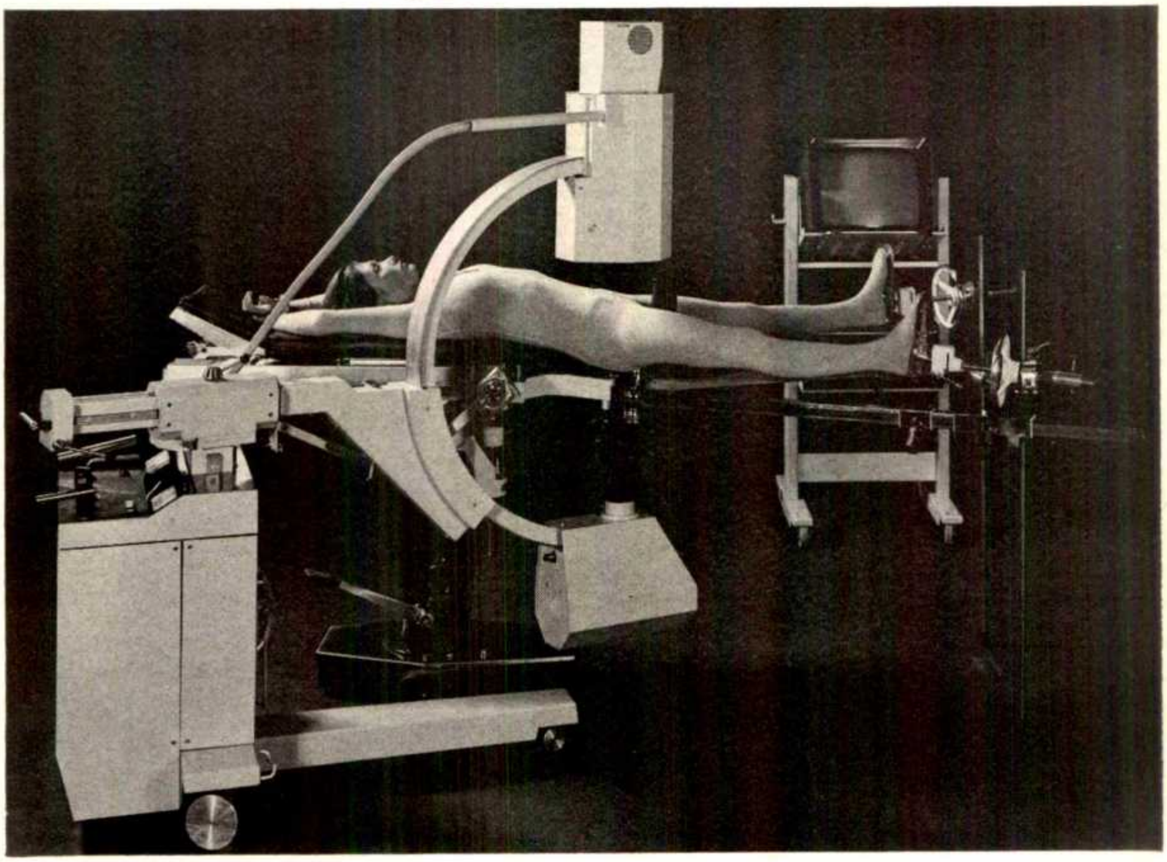

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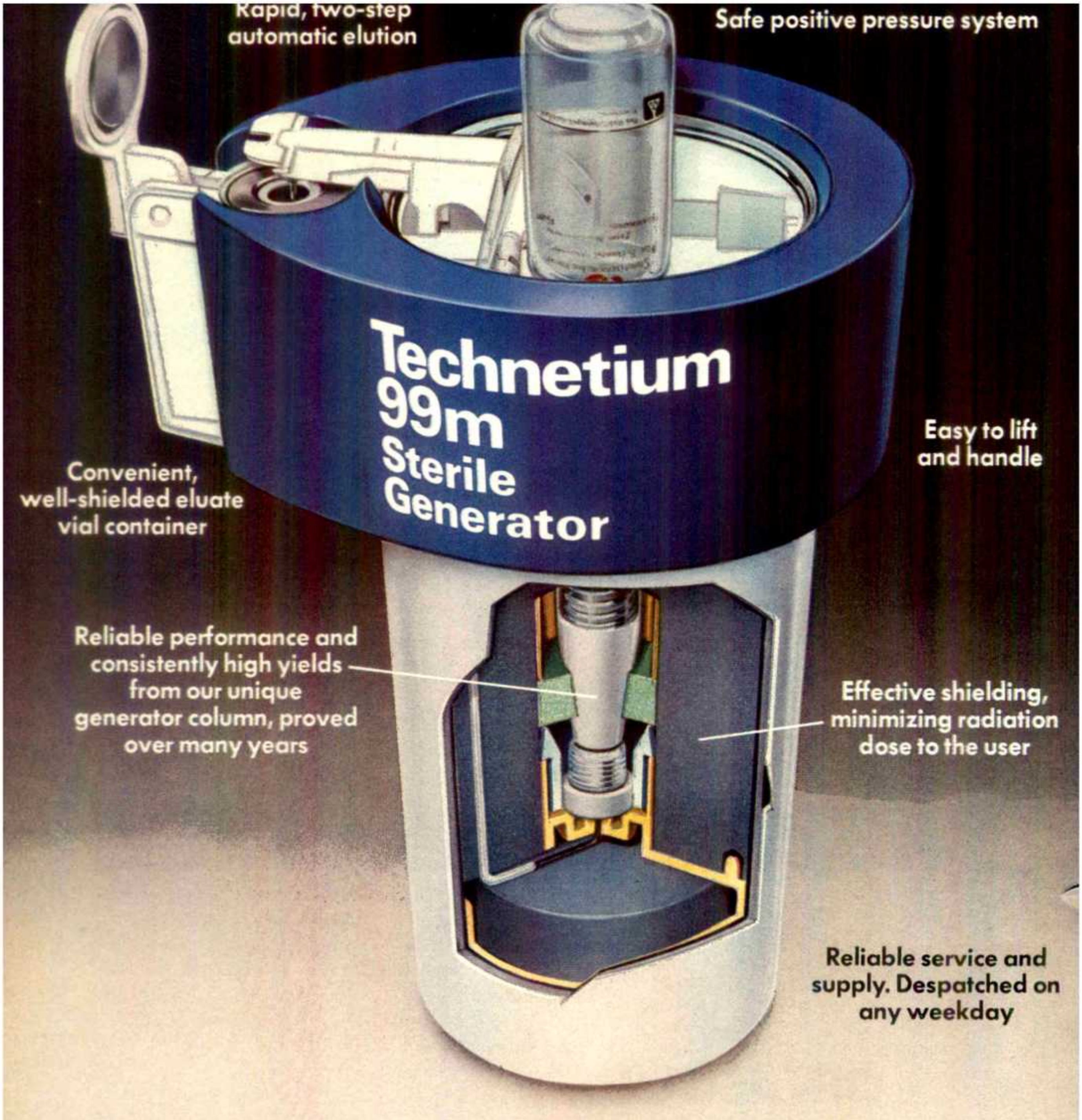
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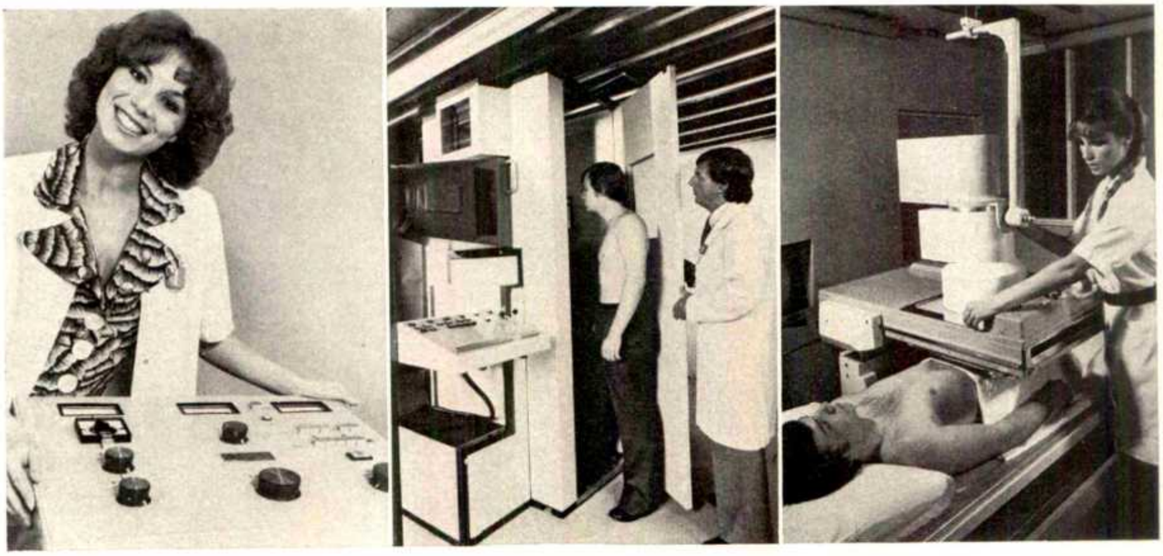

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—from the *Guardian* 13.1.1978.

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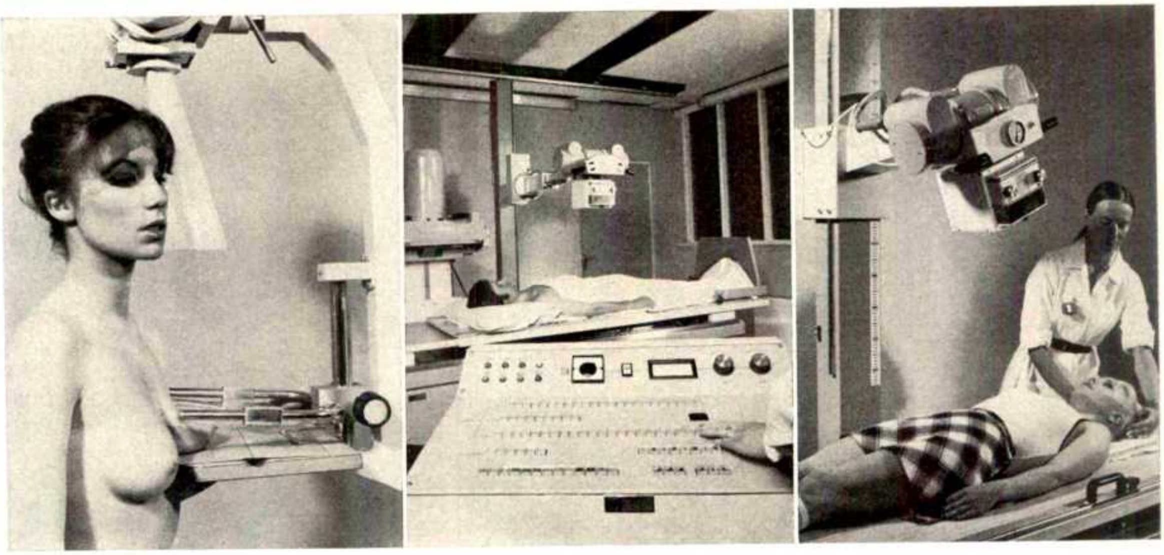

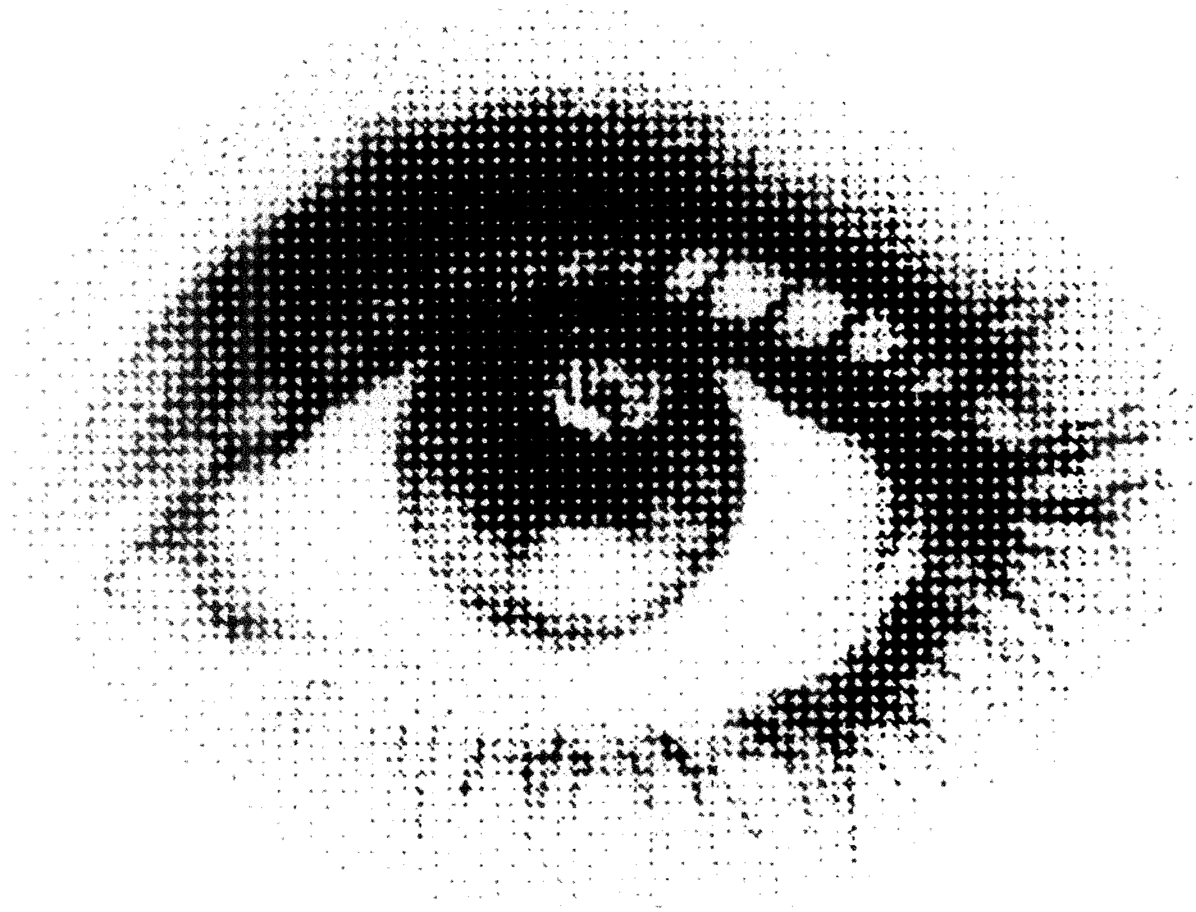

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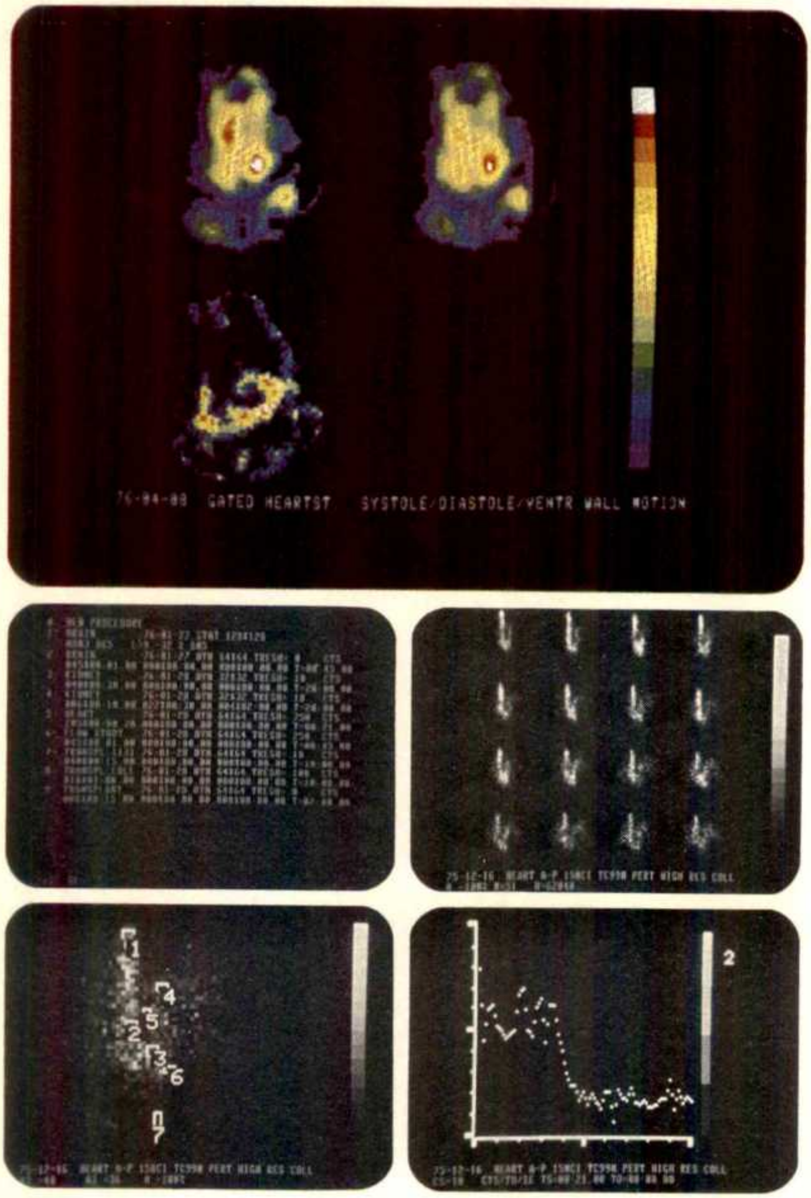
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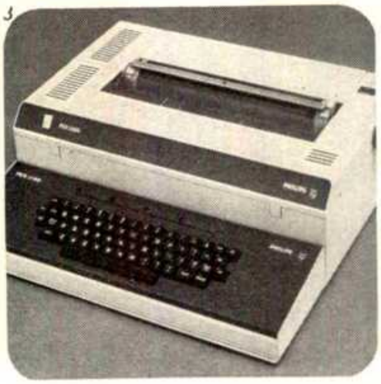

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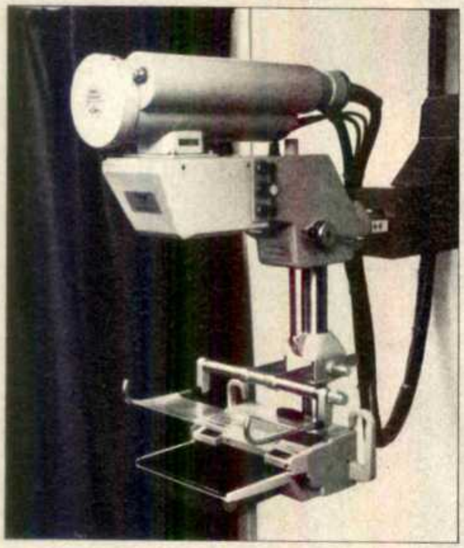

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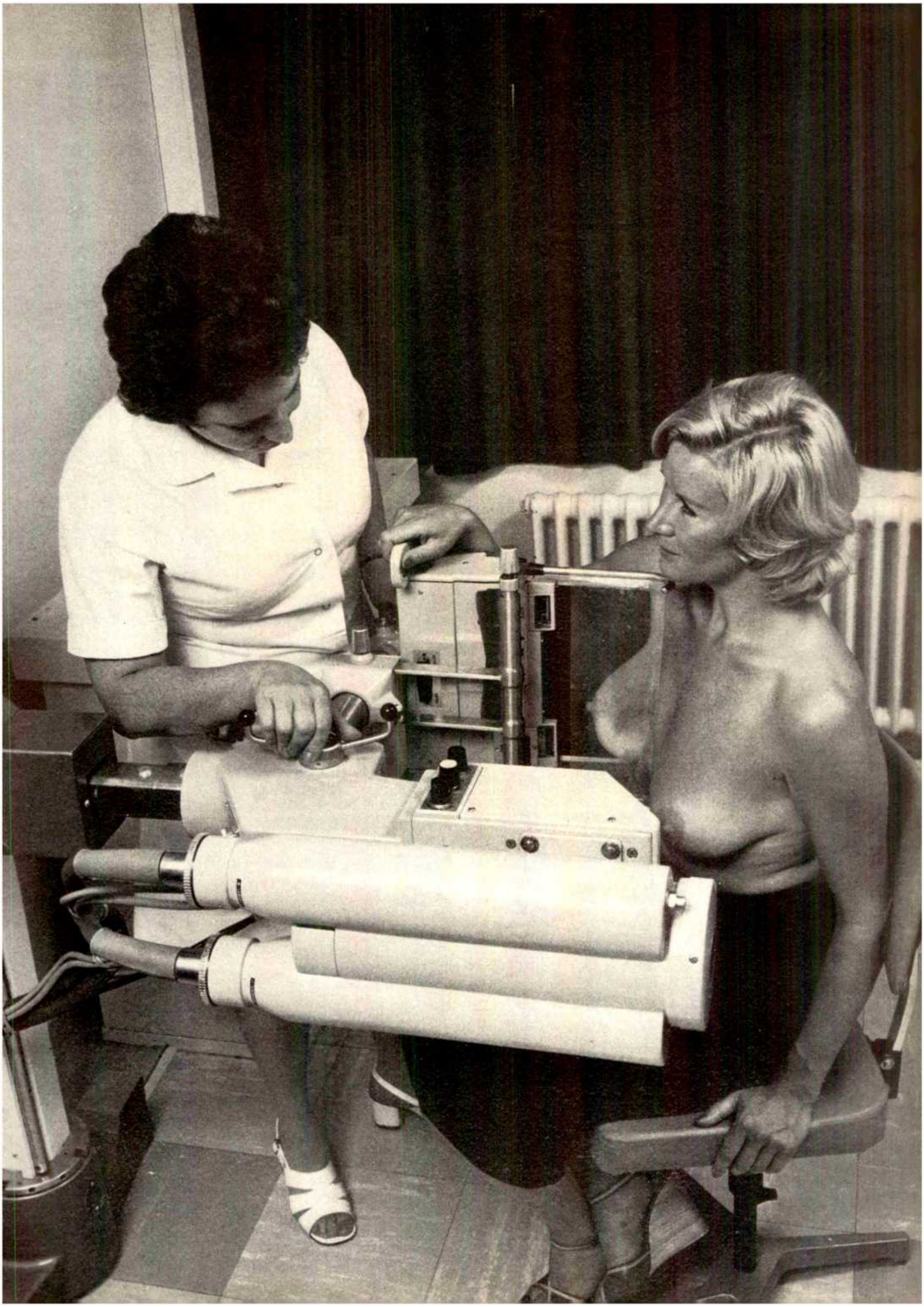

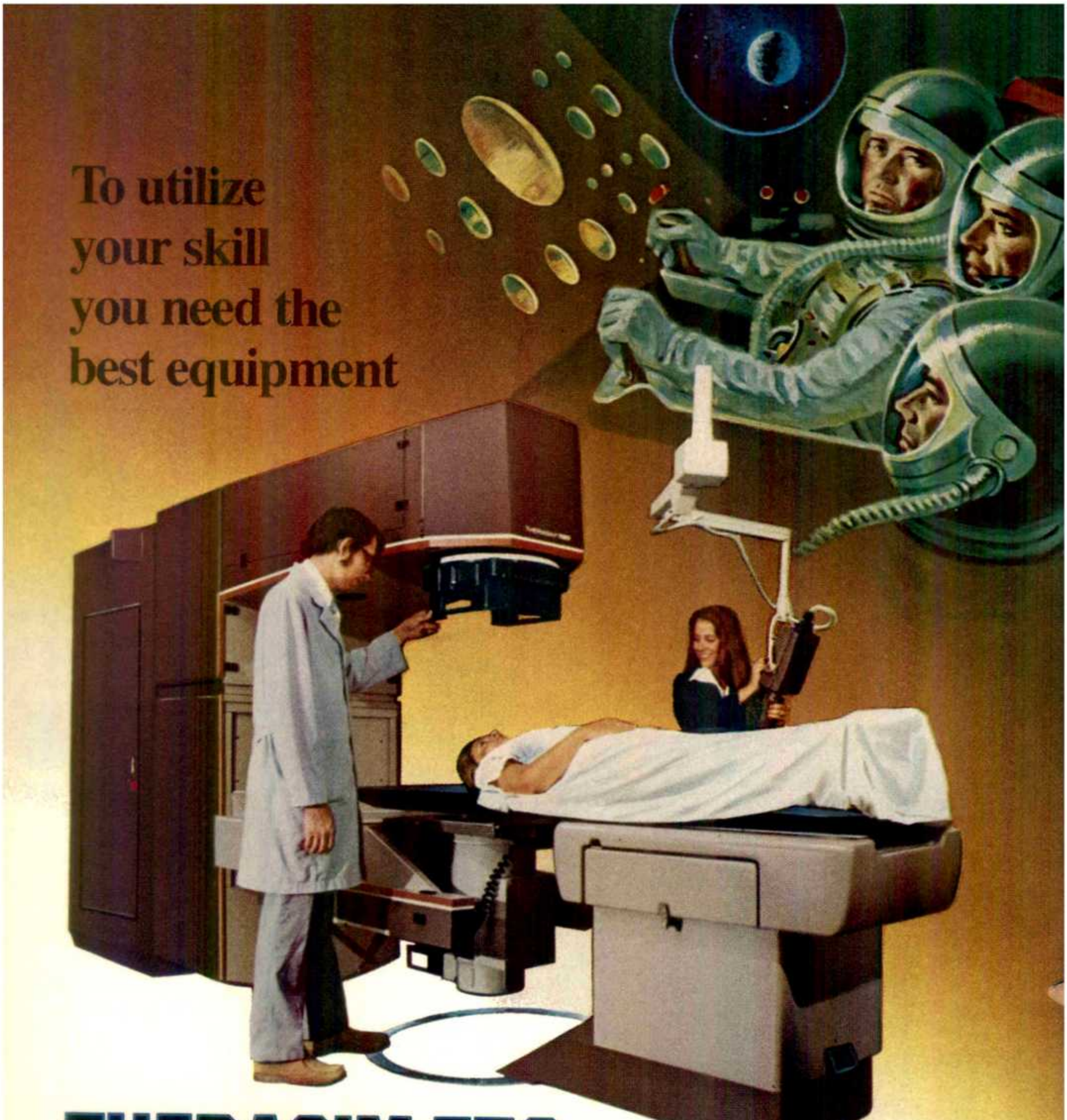

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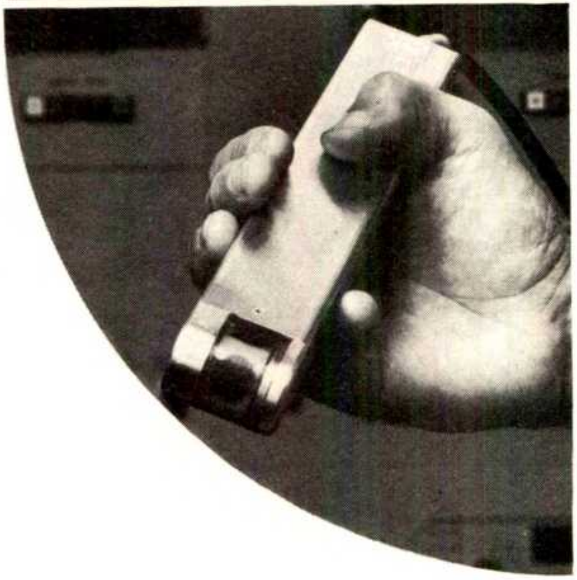

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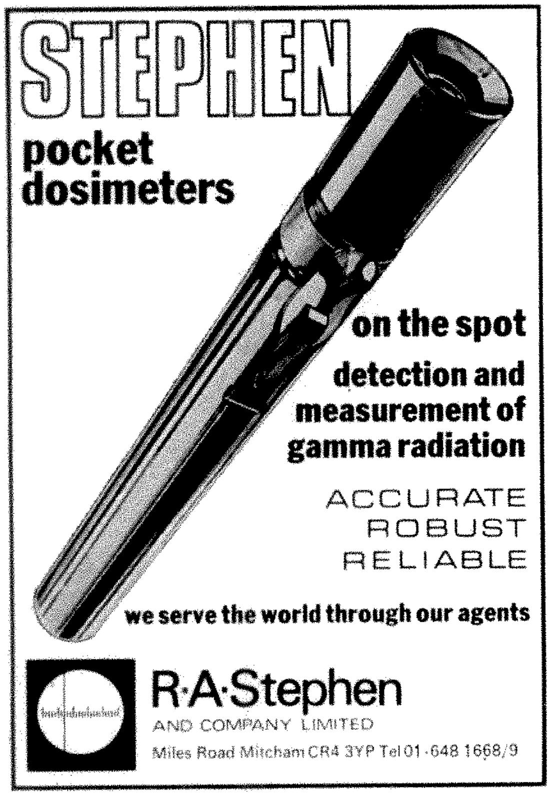

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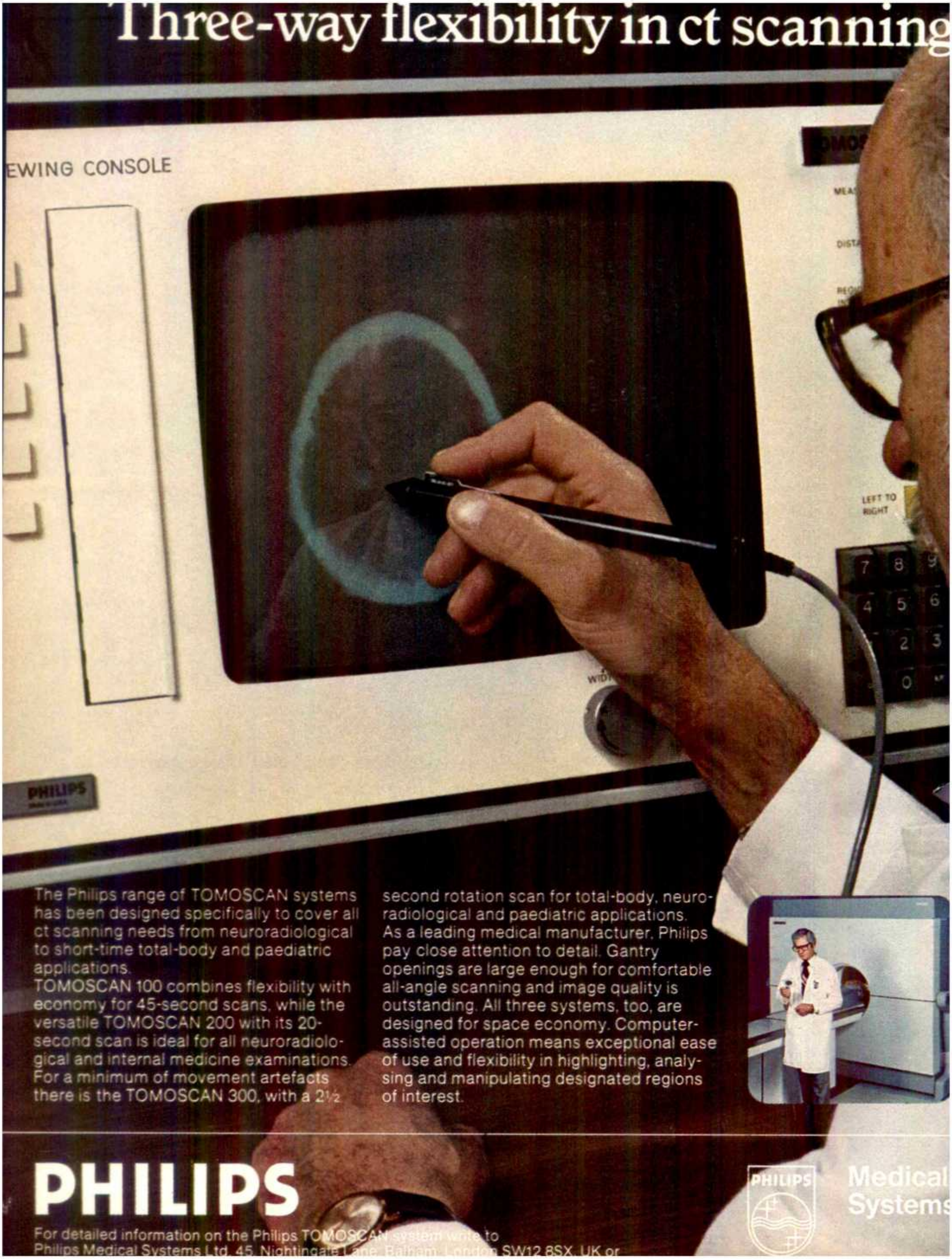

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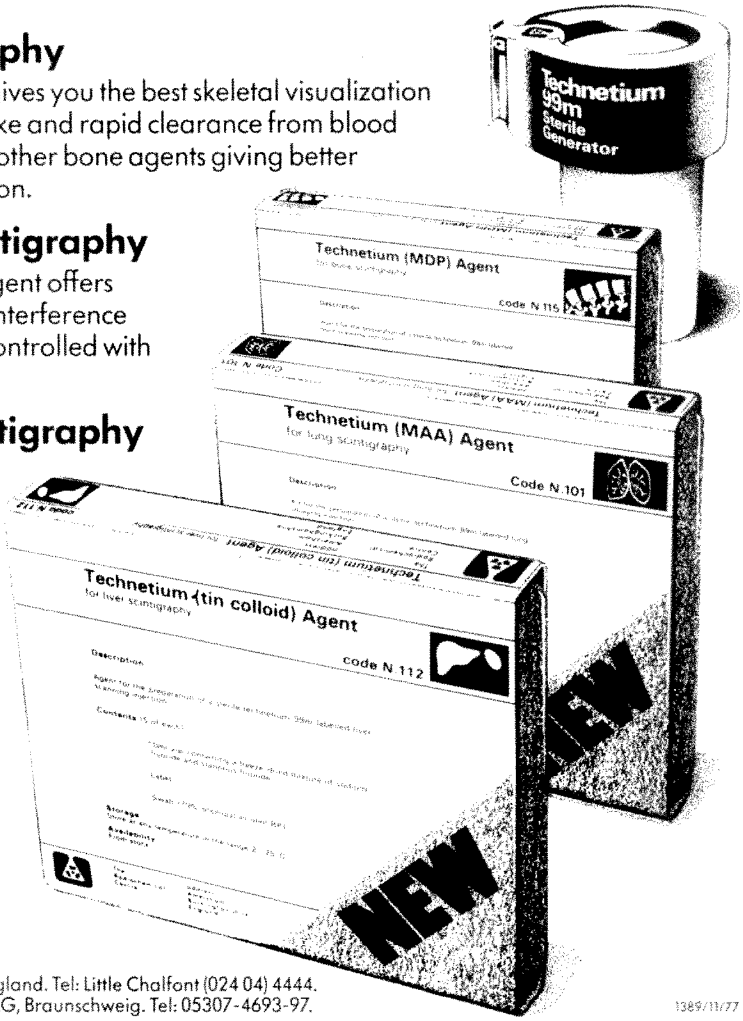

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121 figures, 70 tables. XII, 317 pages. 1975
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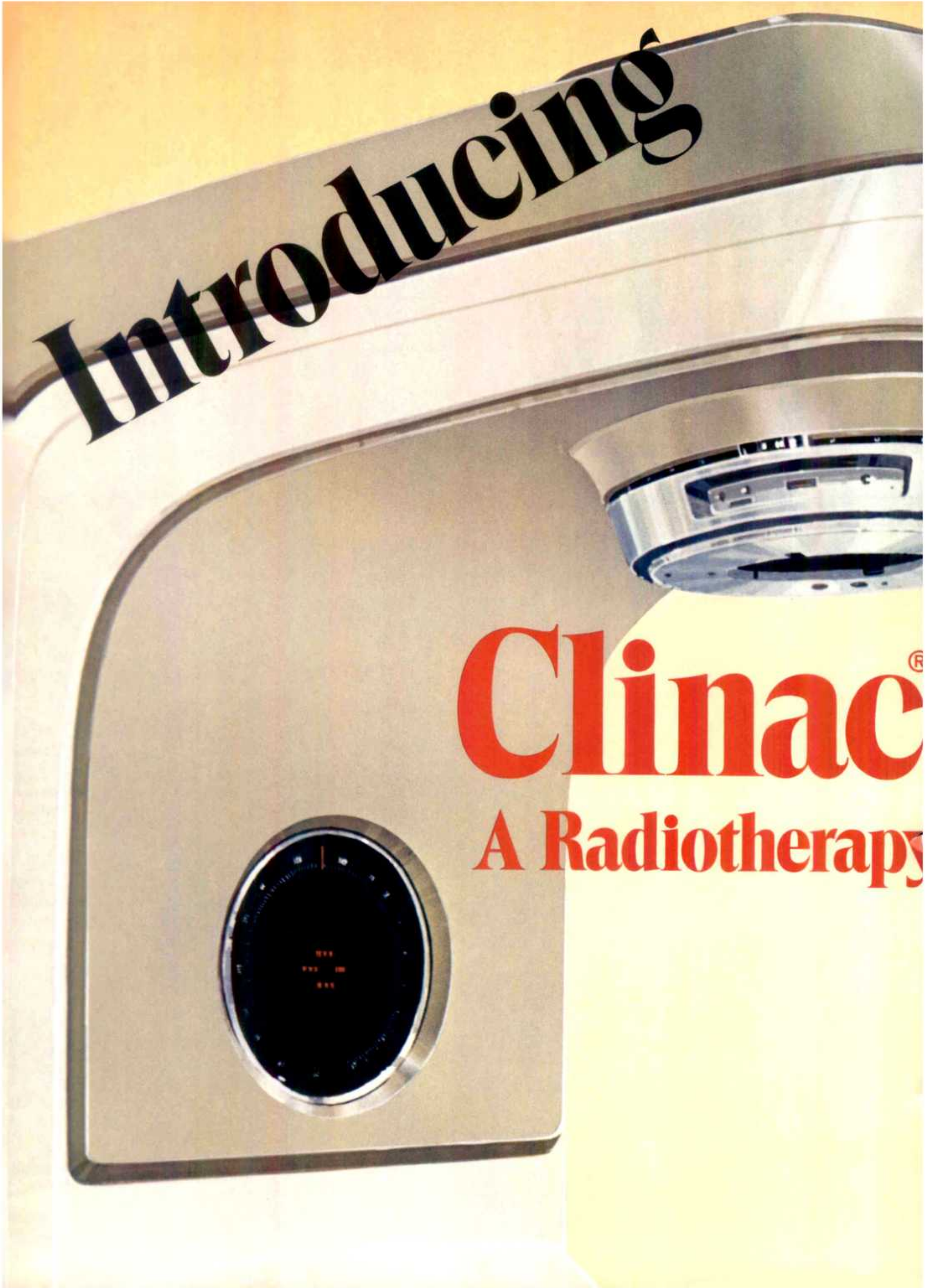
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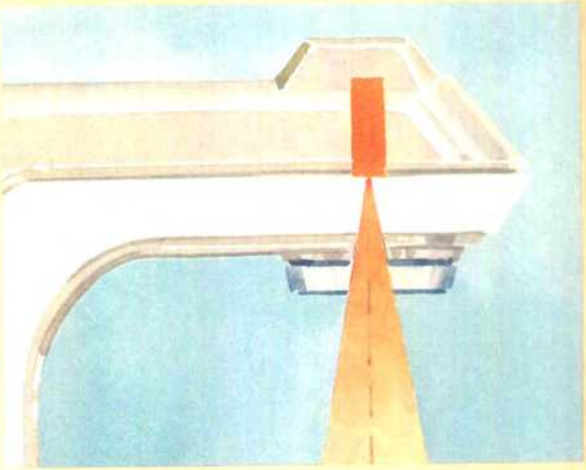

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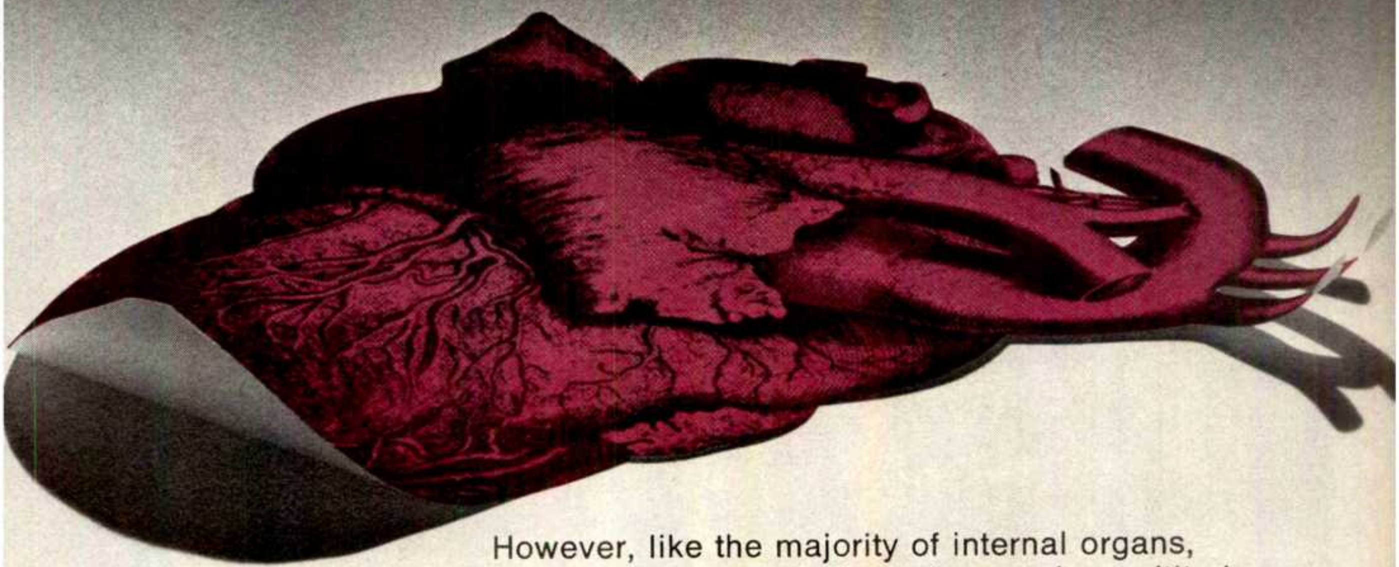

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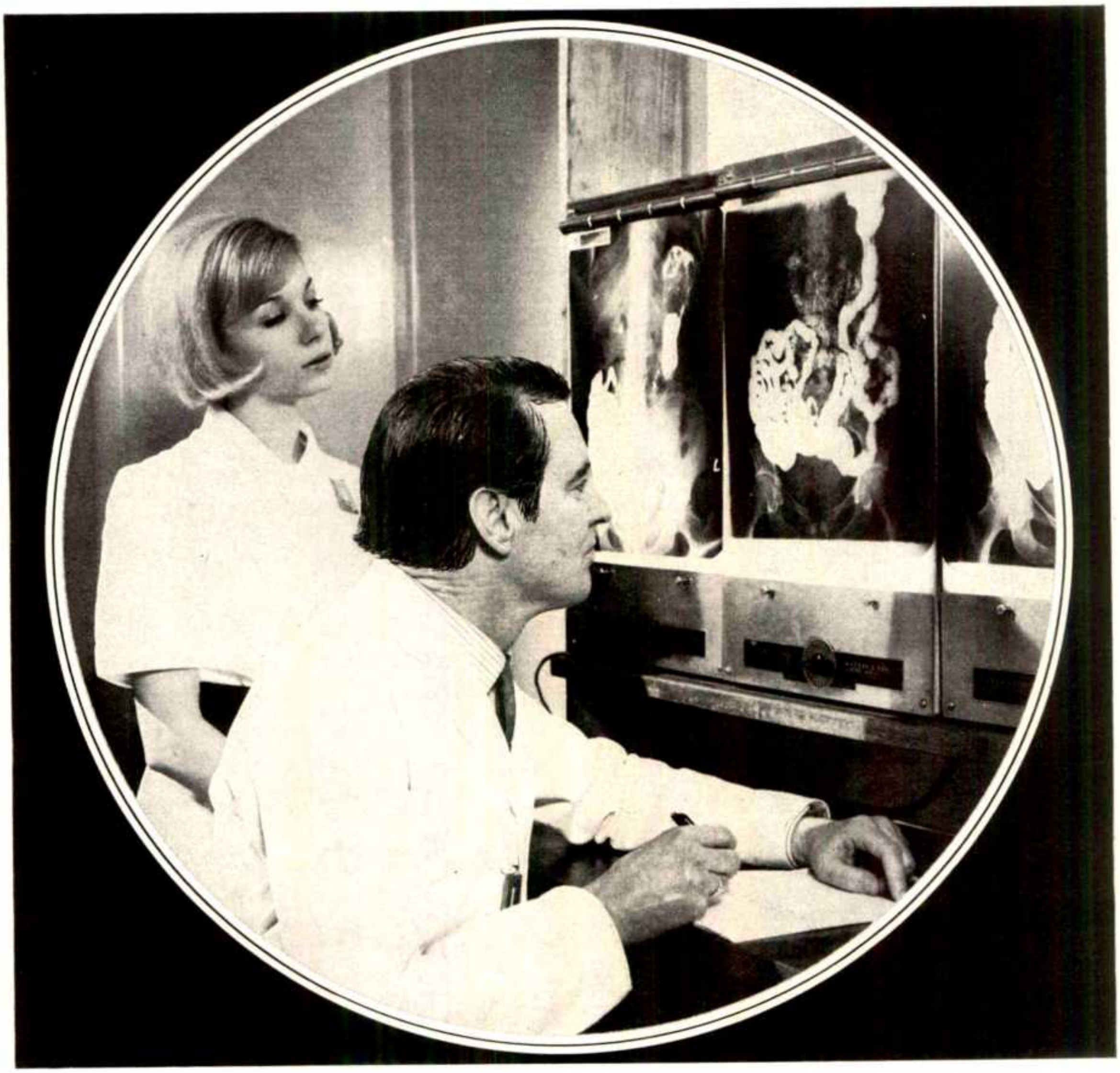

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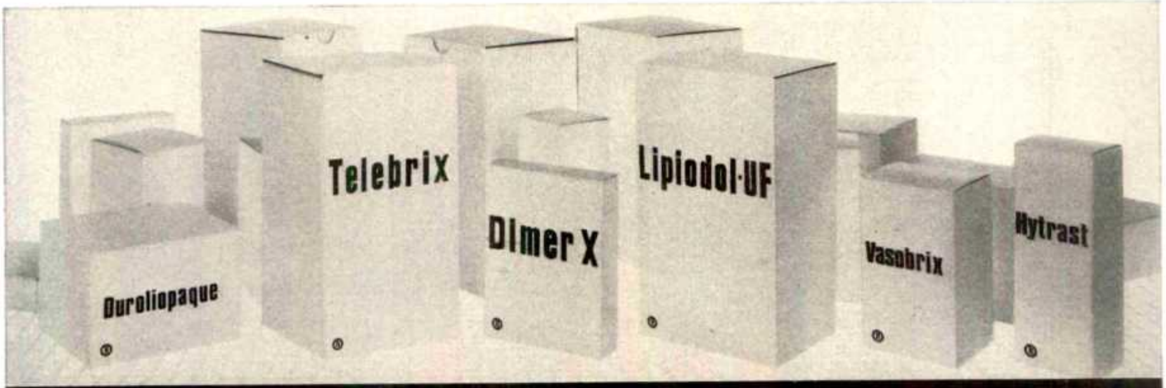

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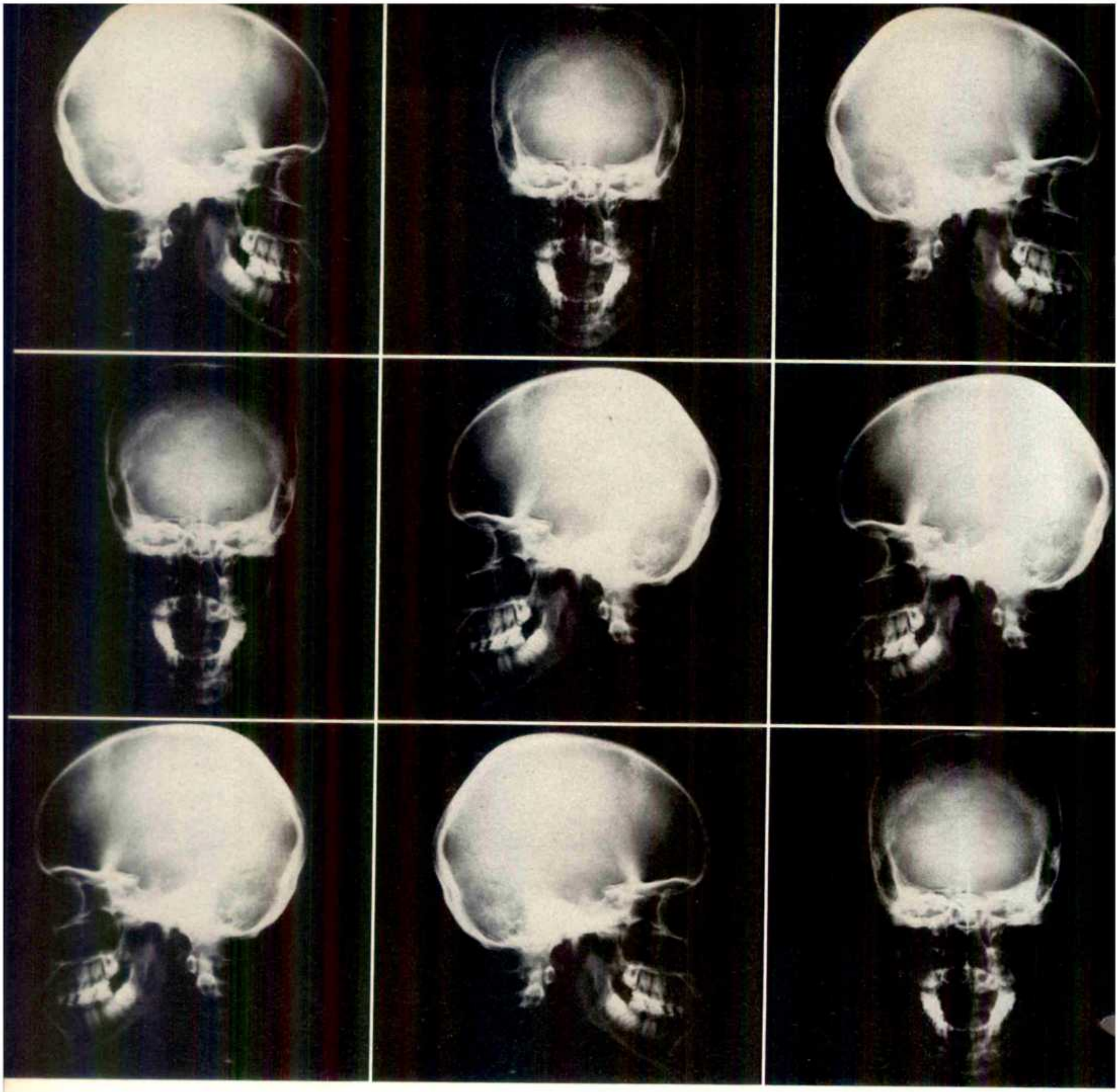

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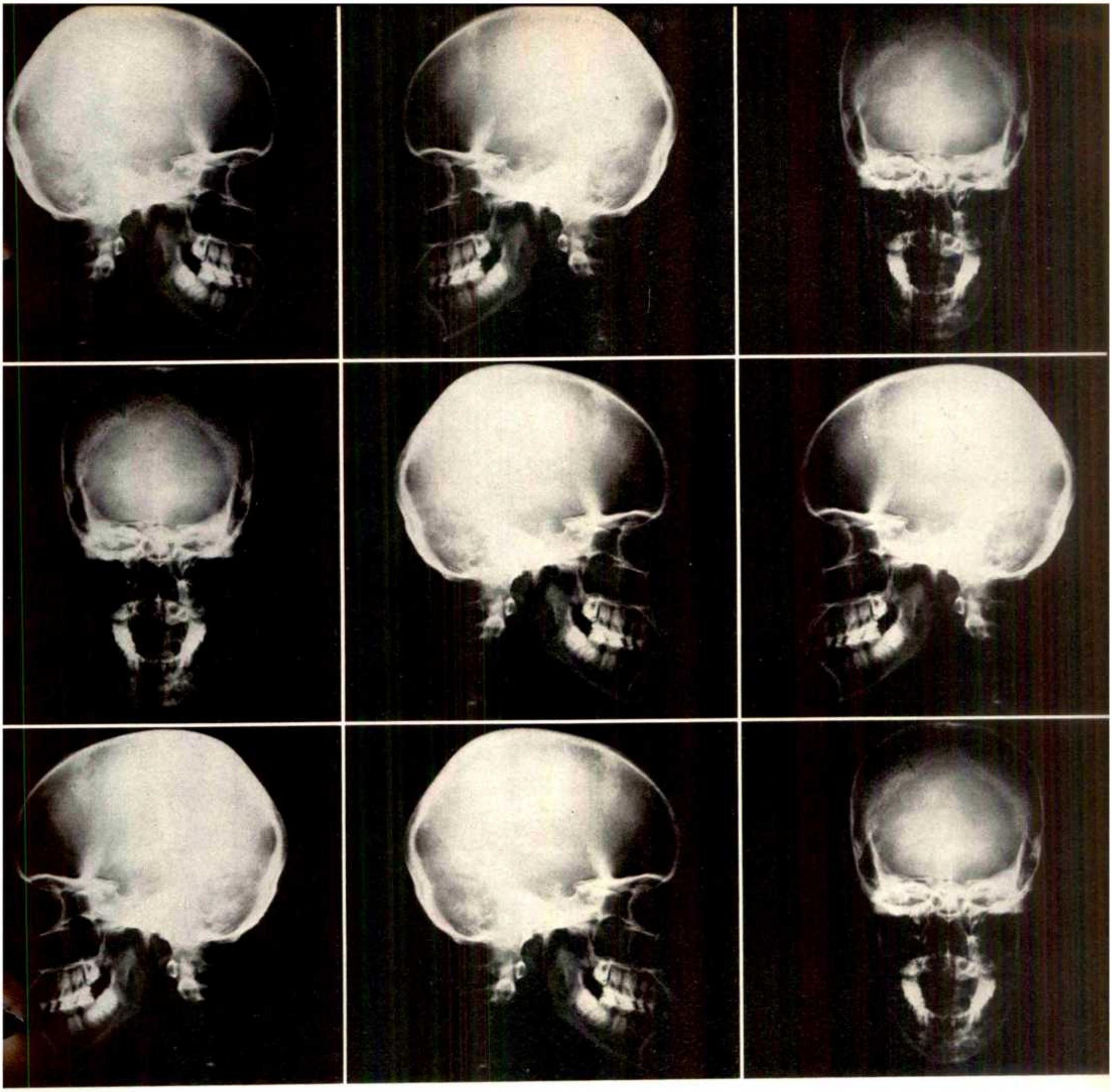

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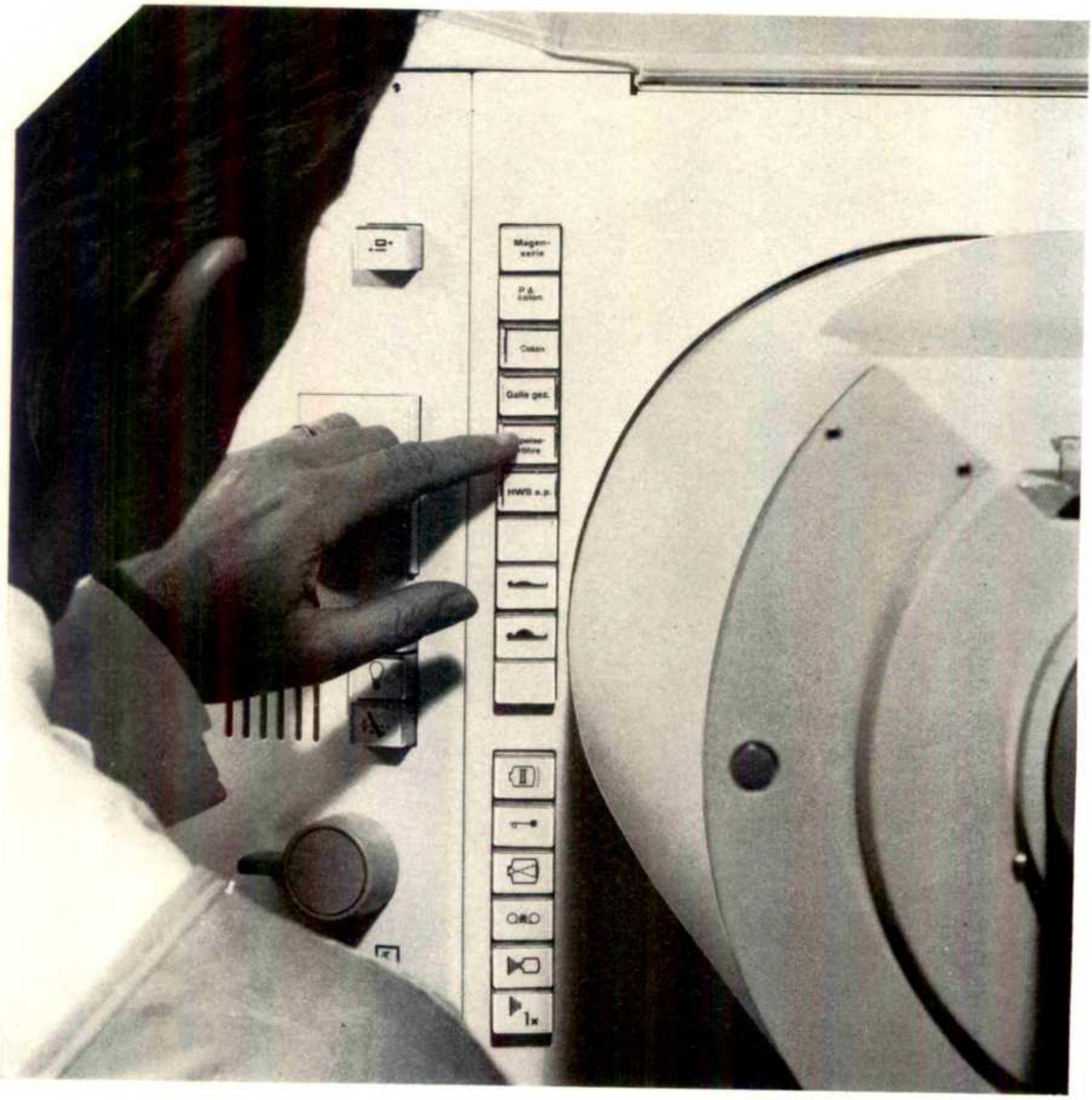

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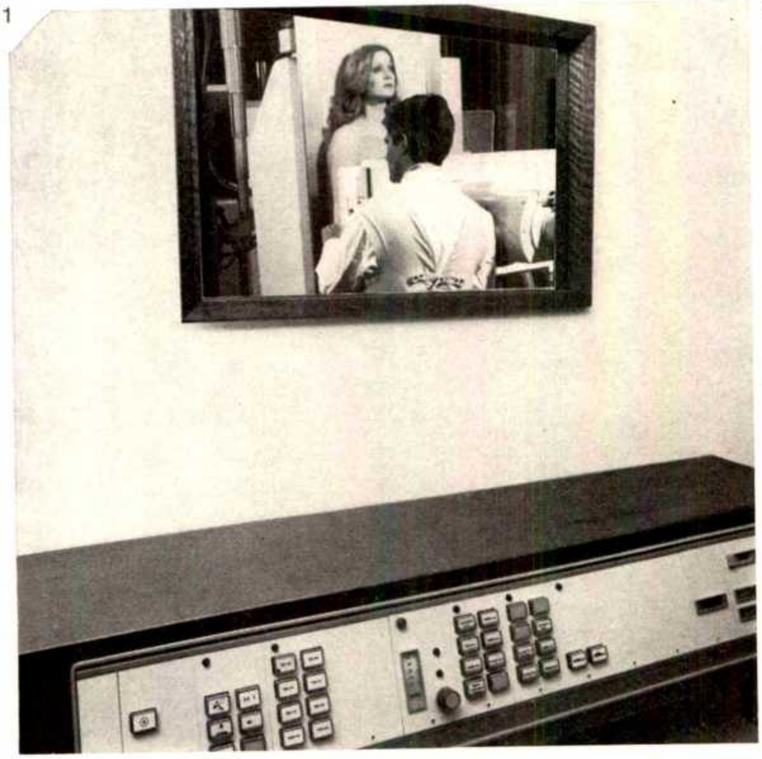

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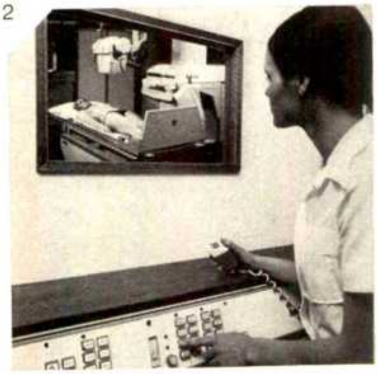

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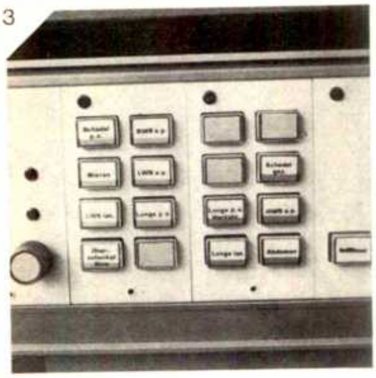

4

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ANNOUNCEMENT

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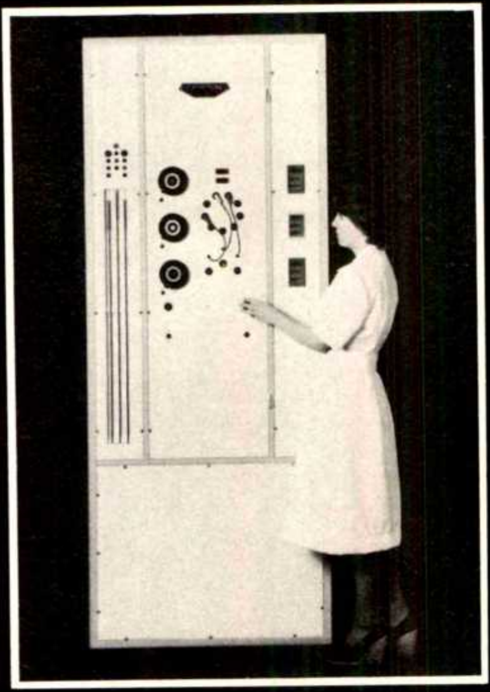

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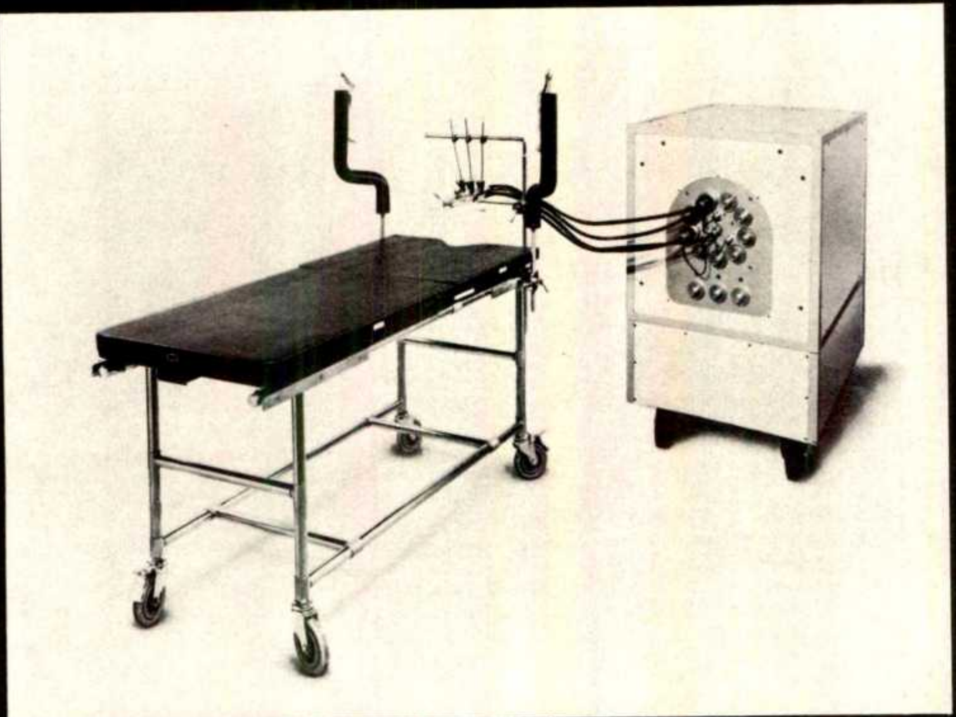

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The British Journal of Radiology

Review article

Classification and radiographic features of uterine malformations: hysterosalpingographic study

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(*Received April, 1977*)

ABSTRACT

A series of 13470 hysterosalpingographic investigations demonstrated congenital uterine malformations in 1160 cases (8.6%). Uterus arcuatus and uterine hypoplasia, the latter ranking as a malformation on embryological grounds, together accounted for two-thirds of the cases, uterus unicornis unicollis and uterus bicornis unicollis together for over a quarter and the others, uterus didelphys, uterus bicornis bicollis and uterus septus/subseptus, for much smaller percentages. Each malformation is described and illustrated by typical hysterosalpingograms. In addition to its decisive importance in diagnosis, hysterosalpingography is also valuable in planning surgical correction in many cases.

Our study of congenital uterine malformations is based on over 20 years' experience. 13470 hysterosalpingographic investigations disclosed 1160 malformations or 8.6%, with the breakdowns as shown in Table I.

Hysterosalpingography, at first used only in the study of tubal patency and function in sterility, is now regarded as a basic investigation in the diagnosis of female genital tract diseases, for it reveals the site, position, morphology, size and configuration of the uterine cavity and tubes. Roentgencinematography completes the radiological pattern with data on the mobility of the uterus, distensibility of its walls, tone and motility of the Fallopian tubes.

The choice of contrast medium is still a difficult problem, despite the wide range of available products. Two groups of radiopaque media at present hold the field: iodized oils and water-soluble organic iodine compounds. We prefer the former in the majority of cases.

TABLE I

Cases	Type of malformation	% of all malformations
158	uterus unicornis unicollis	13.6
18	uterus didelphys	1.5
16	uterus bicornis bicollis	1.4
160	uterus bicornis unicollis	13.8
400	uterus arcuatus	34.5
22	uterus septus or subseptus	1.9
386	uterine hypoplasia	33.3

CLASSIFICATION OF CONGENITAL UTERINE MALFORMATIONS

We propose the following classification based on the embryonic development of the uterus.

1. *Malformations due to arrested development of the Mullerian ducts*

They occur during the first phase of embryonic development, *i.e.* in the phase of craniocaudal growth of the Mullerian ducts. They may be (a) symmetrical or bilateral: uterine aplasia; (b) asymmetrical or unilateral: uterus unicornis unicollis.

2. *Malformations due to failure of fusion of the Mullerian ducts*

The malformations vary according to whether failure of fusion is total or partial: (a) uterus didelphys: resulting from total failure of fusion of the two ducts and characterized by the presence of two vaginae, two cervices and two uterine bodies; (b) uterus bicornis bicollis: resulting from partial fusion of the Mullerian ducts and characterized by the presence of a single vagina with duplication of

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the cervix and uterine body; (c) uterus bicornis unicollis: characterized by the presence of one vagina, one cervix and two quite distinct uterine horns; (d) uterus arcuatus: the least marked degree of failure of fusion.

3. *Malformations from incomplete resorption of the sagittal septum*

(a) uterus septus, due to non-resorption of the sagittal septum, residuum of the primitive duality; (b) uterus subseptus, due to partial resorption of the septum.

4. *Developmental defects of the uterine cavity*

(a) uterine hypoplasia in the strict sense; (b) infantile uterus with disproportion between body and cervix; (c) uterus with gaping cervix and isthmus; (d) pencil uterus; (e) star-shaped uterus.

Uterine Aplasia

Aplasia is the extreme degree of uterine malformation. It can be suspected at gynecological examination through absence either of the vagina or of the ostium; aplasia cannot be detected, for obvious reasons, by hysterosalpingography. It is revealed by air studies (Fig.1).

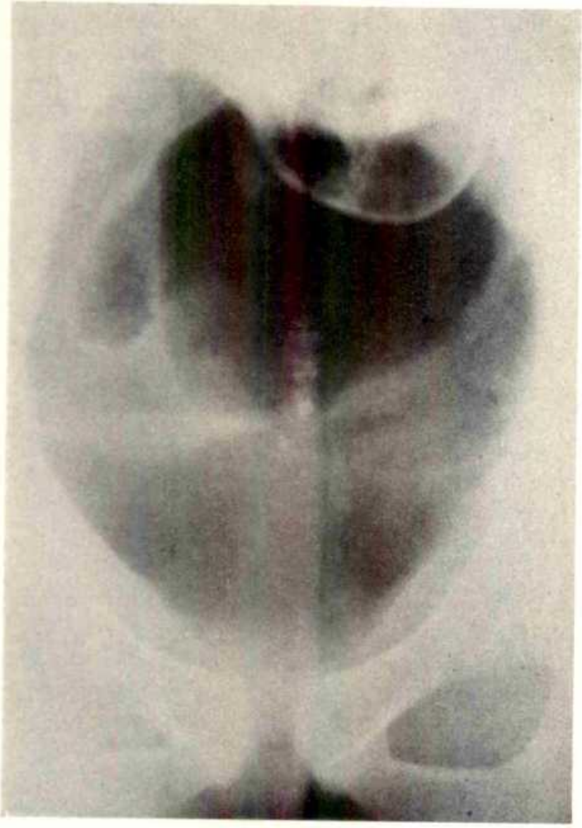


Fig. 1.

Pneumogynegram: uterine and ovarian aplasia.

Uterus Unicornis Unicollis

This malformation occurs during the first stage of the embryo through arrested development of one of the Mullerian ducts and is characterized by one cervix and a single uterine horn, from the tip of which the tube originates. The films present three main features: (1) altered morphology of the uterine cavity, which appears as a fusiform opacity with a mainly longitudinal diameter; (2) lateral deviation of the uterus in the pelvis; (3) presence of a single tube.

A typical example of this malformation is shown in Fig.2: the normally-developed uterine horn is

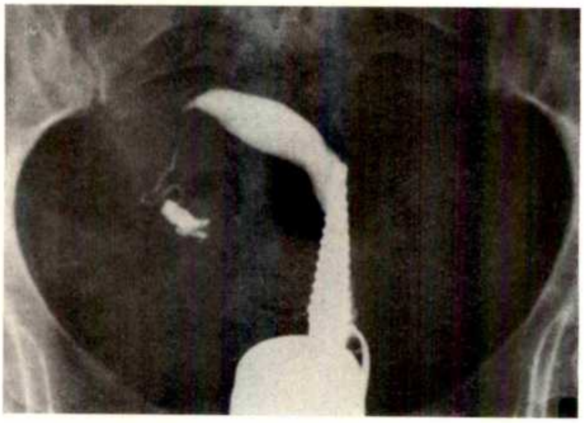


Fig. 2.

Uterus unicornis unicollis. Note the markedly increased diameter of the cervical canal.

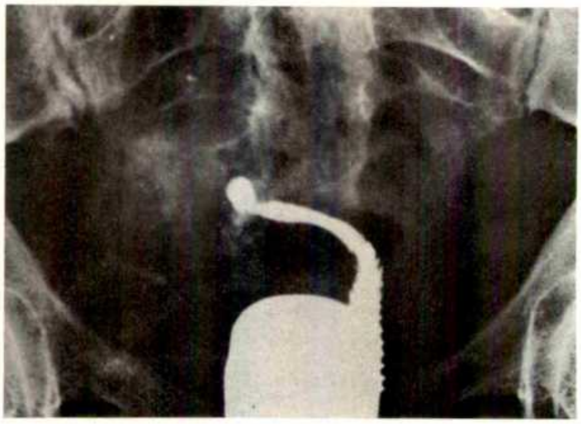


Fig. 3.

Uterus unicornis unicollis with marked hypoplasia. Dilatation of the cervical canal.

deviated to the right; the corresponding tube is patent. Urography, mandatory because of the common embryological origin of the urinary and genital tract, showed agenesia of the left kidney in this case. In addition to the spindle shape, there are other forms of uterine horn, such as the one shown in Fig.3, where the uterus is decidedly small and shaped like an elongated cylinder. A single-horn image on the film is not enough to rule out the presence of the other horn, which may exist but be rudimentary and uncanalized or lack an ostium, thus preventing passage of the contrast medium. A case in point is Fig.4: the X ray film shows a uterus unicornis unicollis with good tubal patency but laparoscopy demonstrated the presence of an uncanalized rudimentary contralateral horn. In this connection we cite the opinion of some workers to the effect that medialization of the normally-developed horn may be an indirect sign of the presence of a rudimentary horn in cases in which the latter is joined to the former in its upper portion.

UTERUS DIDELPHYS—UTERUS BICORNIS BICOLLIS

These malformations, caused by more or less completely arrested fusion of the Mullerian ducts, are alike in having duplication of uterus and cervix but differ in the morphology of the vagina, which is double in uterus didelphys and single in uterus bicornis bicollis.

Figure 5 shows an opacified left uterine horn, which is well developed and deviated to the left side of the pelvis; the tube arising from it filled normally. Figure 6 shows the right horn lying longitudinally on the mid-line of the pelvis and a distinctly spastic isthmus. This is the most typical pattern of a double uterus.

Figure 7 depicts a rare pattern of incomplete uterus didelphys. The uterus is H-shaped with two completely independent cervical canals, giving rise to two uterine cavities of quite different shape and size, communicating at the base of the two horns: the left cavity is definitely undersized and has a leftward transverse lie in the pelvis; the other, of normal size and slightly deviated to the right, presents a marked filling defect which occupies the entire cranial portion of the horn, thereby preventing communication between the uterine cavity and the corresponding tube.

According to our case-material fertility in women with double uterus is often normal, which is not the case with other uterine malformations. It has, in

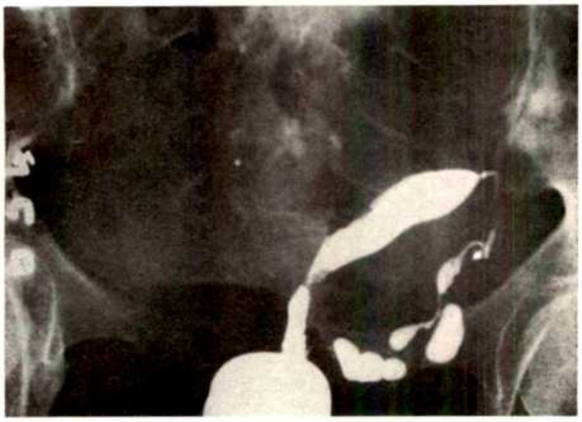
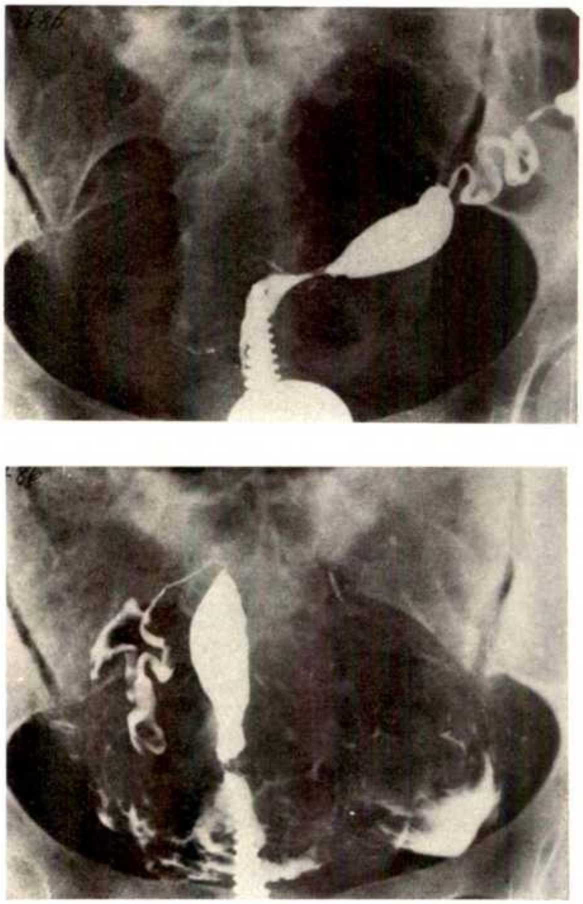


FIG. 4.

Uterus bicornis unicollis with atresia of the right uterine horn, not visualized at hysterosalpingography but found at laparoscopy. The left uterine horn, which is well developed, presents an irregularity of the left margin of its middle portion, probably due to the insertion of the atretic horn.



FIGS. 5 and 6.

Complete uterus didelphys. In this investigation the uterine cavities were opacified in two stages, first the left and then the right. Both horns are normally developed.

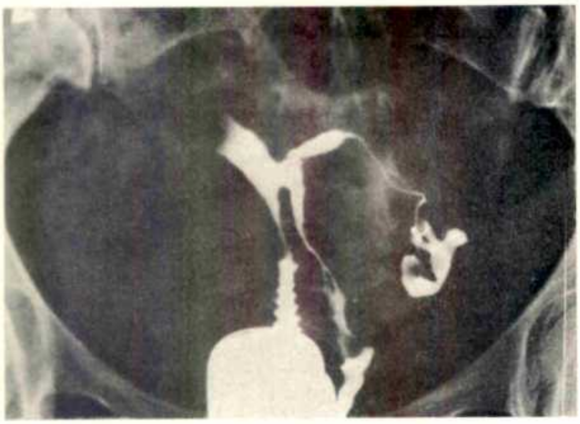


Fig. 7.

Incomplete uterus didelphys. Filling of the cervical canals in successive stages: the ample communication between the two uterine horns, however, permits simultaneous visualisation of both cavities and both cervices. Marked hypoplasia of the left uterine horn, which is anteversoflexed. The morphology of the right uterine horn is altered, the distal portion being mutilated by a submucous fibromyoma at the tip.

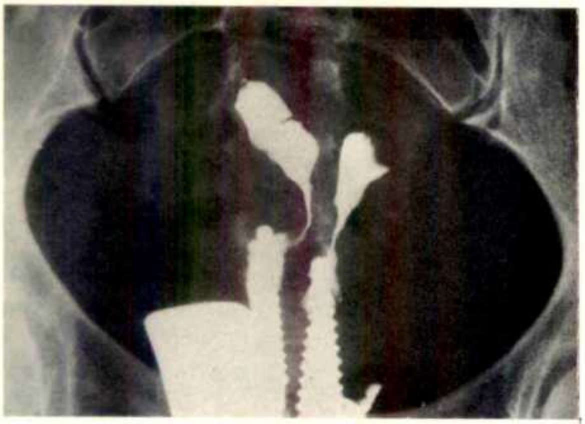


Fig. 8.

Incomplete uterus didelphys. Simultaneous filling of the two uterine cavities by means of two injectors. Hypoplasia of the left uterine horn with altered morphology due to the presence of submucous fibromyomas at the tip. Mild hypoplasia of the right uterine horn with an embryonal fimbria on the middle portion of its profile. Small submucous fibromyoma in the intramural portion of the right tube. Bilateral tubal occlusion.

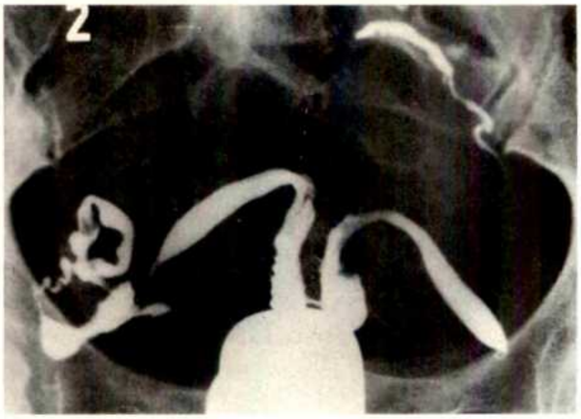


Fig. 9.

Uterus bicornis bicollis. Marked dilatation of both cervical canals. Anteroversoflexion of the uterine horns, which are definitely elongated.

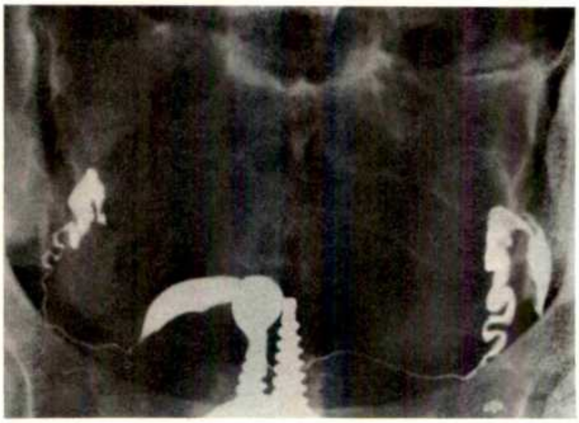


Fig. 10.

Uterus bicornis bicollis. Hypoplasia and atonia of the right uterine horn. Marked tonus of the left uterine cavity, which is deviated to the right.

fact, been possible to show that sterility is due not so much to the malformation *per se* as to associated factors. We quote as example the case of Fig.8, which refers to a woman, married for three years and admitted for investigation of sterility. The patient was subjected to hysterosalpingography after clinical examination had demonstrated the presence of a septum 1 cm from the vestibule of the vagina. The X-ray film shows two quite separate cervical canals and two club-shaped uterine cavities with a mainly longitudinal diameter occupying the central portion of the pelvis. About halfway down the left wall of the right cavity is a transverse stria, probably related to an embryonal fimbria. The tubes were not visualized and the contrast did not pass into the peritoneum. In this case therefore sterility was due to bilateral tubal occlusion at intramural level.

Less frequent morphological features but highly important ones because of their relevance to the problem of spontaneous abortion are shown in Figs. 9 and 10. Figure 9 refers to uterus bicornis bicollis of a young woman who had had two spontaneous abortions: the film shows the abnormal length of the cervical canals, which are also considerably distended; they are followed by two uterine horns extending downward and to either side of the pelvis. In this case the repeated abortions seem to have been due to the gaping of the cervix and isthmus, which prevented retention of the embryo in the uterine cavity. Figure 10 illustrates another case of uterus bicornis bicollis: the left horn, of normal size, has a transverse lie towards the right side of the pelvis; the right horn, roundish and under-sized, lies on the mid-line. Tubal patency is well conserved. Clearly, in this case it was underdevelopment of one cavity that prevented the normal course of pregnancy. The figure reveals another, functional, feature of double uterus: the independence of the two uterine cavities in terms of kinetic function. There is a detectable difference of tone between the two horns: the right horn, in the mid-line, is atonic whereas the left horn, deviated to the right side, presents definite contractions.

UTERUS BICORNIS UNICOLLIS

This malformation is due to arrested development of the portions of the Mullerian ducts destined to form the uterine body and is characterized by the presence of a single cervical canal and two quite distinct uterine bodies. Clinical examination is unlikely to demonstrate the condition because there are no changes in the vagina or cervical canal; bimanual palpation may prompt suspicion on the ground of two masses found in the pelvic region, although fibroid is then more likely. We consider the diagnosis of uterus bicornis unicollis can only be clinched by the finding of these features on the X ray film: (1) separation of the two horns at isthmus level; (2) presence of a wide angle between the horn images; (3) fusiform appearance of each horn with convexities of the margins.

These features appear in Figs. 11 and 12.

Figure 11 represents the most typical pattern of uterus bicornis unicollis. The two uterine horns separate at the level of the isthmus, the right horn deviated to the right and the left in a more central position. The cavities, slightly smaller than normal, are elongated and taper off towards the tips, from which the well-filled tubes arise.

The case illustrated in Fig. 12 shows two uterine cavities dividing at the isthmus to form a fairly obtuse angle facing upward. Both cavities are directed laterally, in keeping with the embryonal disposition of the Mullerian ducts: one to each side of the pelvis. The cavities differ markedly in size, as often occurs in this malformation: the right cavity is slightly undersized while the left is well developed with a fair degree of atonia. The tubes continue immediately from their tips, the left tube being well filled and the right only in its inner portion.

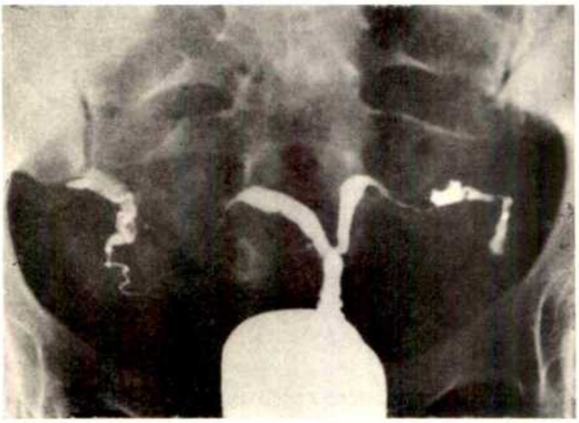


FIG. 11.

Uterus bicornis unicollis. Hypoplasia of both uterine cavities.

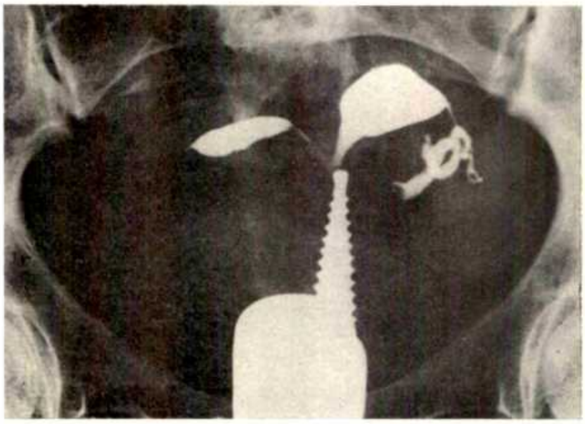


FIG. 12.

Uterus bicornis unicollis. Hypoplasia of the right uterine cavity. Transverse diameter of the left uterine cavity increased through atonia.

The patterns described correspond to a model of uterus bicornis unicollis that often undergoes variations, especially at the cervical canal. In Fig. 13 the uterus is Y-shaped. The cervical canal is decidedly distended and from its cranial end the two uterine horns arise, clearly splayed, each directed towards its own side of the pelvis. Both cavities are club-shaped but differ in size, the left being smaller than the right. The tubes, poorly filled, allow very little contrast medium to pass into the peritoneum.

In Fig. 14 the cervical canal, slightly leftward bound, irregularly contoured, is enlarged and disproportionately long compared with the uterine horns. These differ in shape and size: the right horn, definitely undersized and elongated, continues into the well-contrasted tube; the left horn, larger, though still below-normal in size, presents a large filling defect in the left wall, attributable to a submucous fibromyoma.

In Fig. 15 the cervical canal is still more distended and elongated than in the previous case; further, its course is tortuous and its profile is scalloped. Both uterine horns present several filling defects, attributable to the presence of fibromyomas and embryonal fimbriae which prevent the contrast medium from passing through the tubes, as confirmed in the follow-up X ray.

UTERUS ARCUATUS

This malformation is due to defective fusion of the Mullerian ducts in the fundal area of the uterus, which is thus concave. It is almost impossible to detect clinically or suspect from the history. Only hysterosalpingography shows up the features denoting the presence of uterus arcuatus, namely (1) saddle-shaped fundus; (2) increase in the transverse diameter of the uterine cavity. The pattern is shown in Fig. 16. The fair-sized uterine cavity is

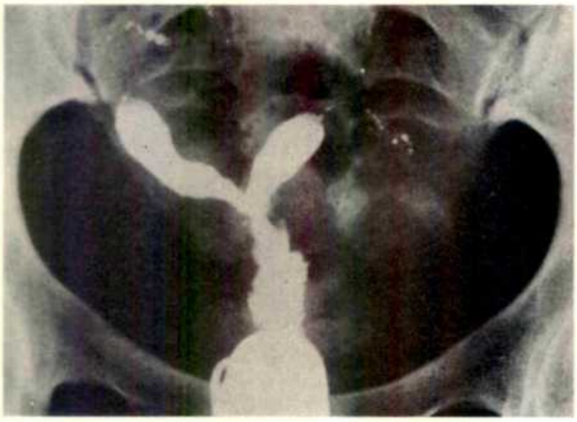


FIG. 13.

Uterus bicornis unicollis. Dilatation of the cervical canal. The morphology of the tips of both uterine horns is altered by fibromyomas, responsible for bilateral tubal impatency.

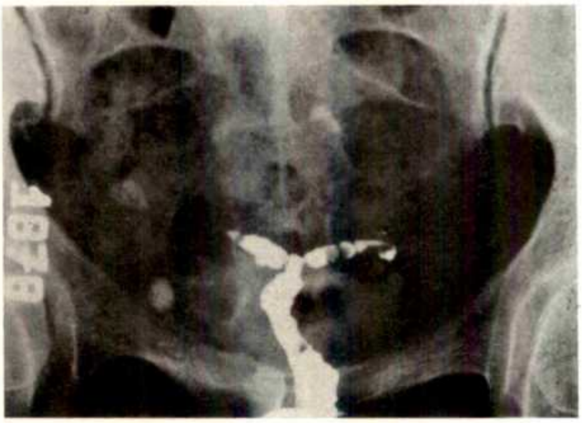


FIG. 15.

Uterus bicornis unicollis. Dilatation of the cervical canal, which is markedly elongated and has a tortuous course. The clearly underdeveloped uterine cavities present filling defects attributable to fibromyomas.

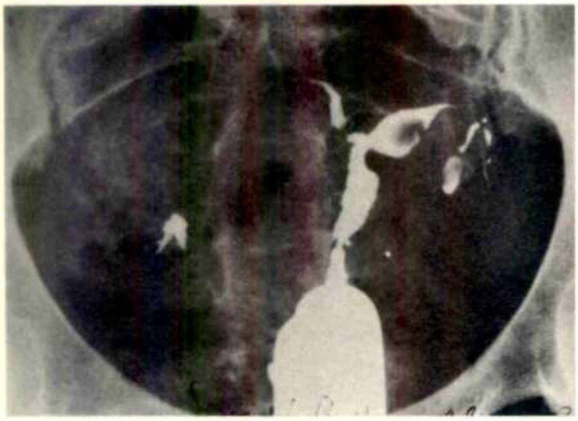


FIG. 14.

Uterus bicornis unicollis. Dilatation of the cervical canal, which is considerably elongated. Marked hypoplasia of the right uterine horn. Filling defect in the left uterine cavity due to submucous fibromyoma.

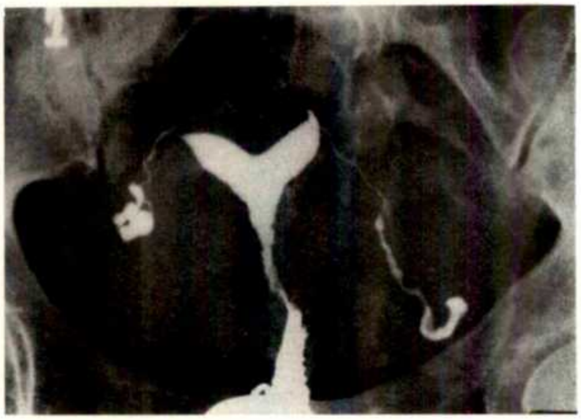


FIG. 16.

Uterus arcuatus. The cervical canal is dilated and elongated and presents numerous notches. Prevalence of the transverse diameter of the uterine cavity; saddling of the fundus uteri.

widened and the outline of the fundus presents a central depression. If this depression is very pronounced, it may be necessary to differentiate it from uterus bicornis unicollis. It is the level of separation of the two horns (high in uterus arcuatus), and the breadth of the fundal depression (an obtuse angle in uterus arcuatus) (Fig. 17) and acute in bicornis, that clinches the diagnosis.

The frequent finding of submucous fibromyomas may create difficulties in diagnosis. When the myoma lies in the central part of the fundus only an air study can resolve the problem. Diagnosis is simpler when growth is asymmetrical, as in the case of Fig. 18, where the fundus uteri shows a wide bowl-shaped concavity, especially on the right side, so that the right horn is displaced and deformed; this asymmetry is due to the presence of a mass (myoma). Figure 19 refers to a case of submucous myoma of the cervical canal capable of giving rise to a pattern similar to that of uterus arcuatus.

Uterus Septus and Uterus Subseptus

Uterus septus is due to total or partial nonresorption of the sagittal septum, residuum of the medial wall of the two Mullerian ducts that failed to come away after ductal fusion. Consequently the external morphology of the uterus is normal but its cavity is divided by a more or less complete septum,

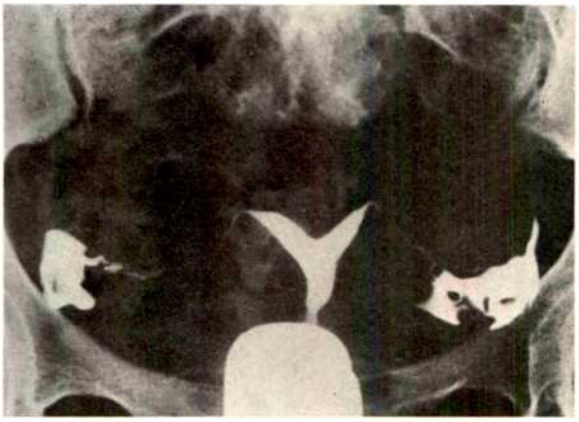


Fig. 17.

Uterus arcuatus. Deep depression of the fundus uteri with high separation of the two uterine horns (differential diagnosis from uterus bicornis).

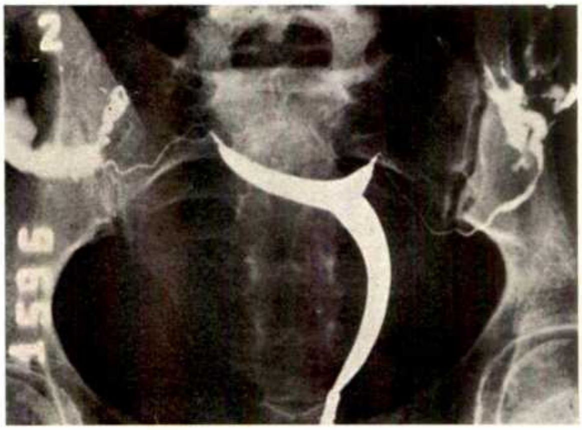


Fig. 19.

Fibromyoma of the cervical canal causing stretching and displacement of the cervical canal on the left side of the pelvis. Deformation of the uterine cavity, which takes on the appearance of uterus arcuatus.

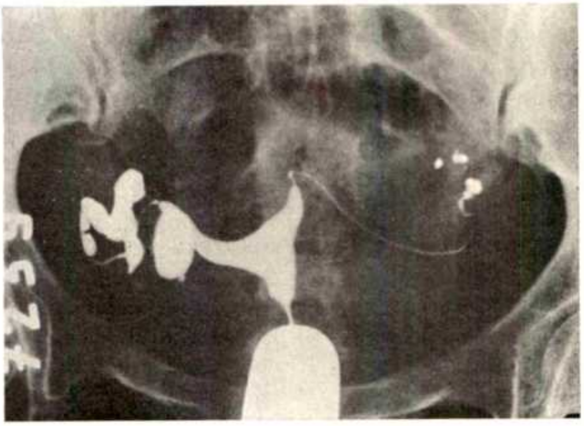


Fig. 18.

Fibromyoma of the fundus uteri causing a large concavity of the fundus, especially on the right side. Differential diagnosis from uterus arcuatus is facilitated by the asymmetry of the cavity.

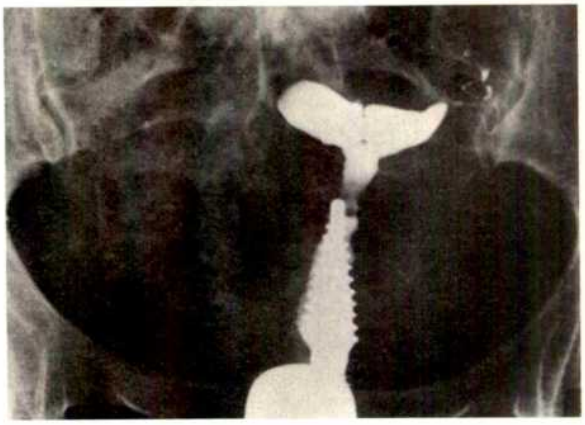


Fig. 20.

Uterus subseptus. Distinctly widened uterine cavity. Profile of the fundus, which is almost straight with a central notch.

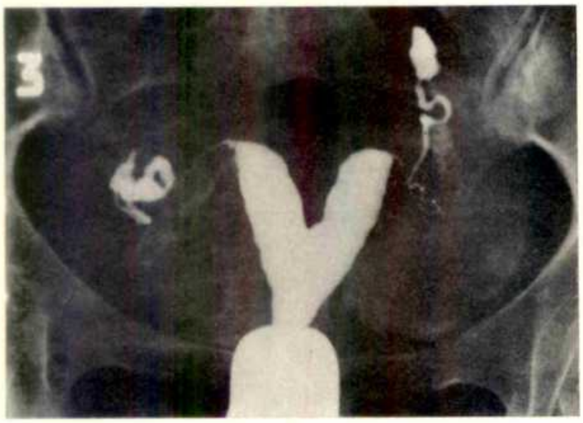


FIG. 21.

Uterus subseptus. Differential diagnosis from uterus arcuatus is based on the acuteness of the angle between the two horns.

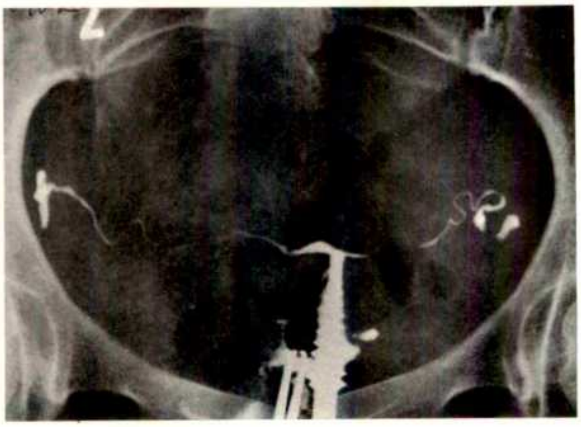


FIG. 22.

Uterine hypoplasia with marked anteversion.

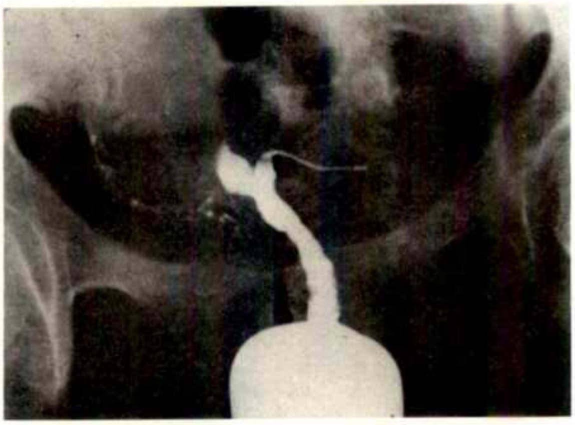


FIG. 23.

Infantile uterus with the cervix too large for the body. The underdeveloped uterine cavity is too wide and divided in its upper portion into two horns.

which is most unlikely to adapt to pregnancy. A completely septate uterus is a rare finding but uterus subseptus is fairly frequent. Its detection is very important because surgical correction ensures very good results. Since clinical examination affords no evidence of this malformation, hysterosalpingography is decisive. A typical case of uterus subseptus is shown in Fig. 20. The profile of the fundus uteri is almost straight with a deep notch in the central portion due to an embryonal rest of the primitive septum. In many cases more extensive separation of the two uterine cavities may give rise to difficulties in differential diagnosis from uterus arcuatus or bicornis. The criterion is the type of angle separating the two cavities, acute (Fig. 21) in uterus septus. Another feature that differentiates uterus subseptus from uterus bicornis is the functional interdependence of the two cavities.

UTERINE HYPOPLASIA

The inclusion of uterine hypoplasia among congenital malformations of the uterus is not universally accepted. However, since the defective development of the uterine cavity is due to lack or loss of hormone production, before birth in the majority of cases, we see no reason for not including uterine hypoplasia among congenital uterine malformations.

Although the uterine cavity is often normal in morphology, this malformation is to be regarded as one of the most serious because it is frequently associated with abnormalities of ovarian or hypophysial function, which account for the high incidence of sterility and alterations of the menstrual cycle in women with uterine hypoplasia.

Uterine hypoplasia in the broad sense is a relatively frequent malformation ranging from high-grade hypoplasia to near-normality. The basic radiographic signs are (1) uterine body of below-normal size; (2) regular triangular morphology (miniature uterus); (3) normal relations between cervix and body; (4) hypertonia and hyperkinesia with frequent spasm of the isthmus. The hypertonia often makes it difficult to evaluate the true capacity of the uterus: another obstacle may be its abnormal position. Marked retroversion or anteversion (Fig. 22), frequently found in uterine hypoplasia, may create difficulties in evaluating uterine volume; in such cases righting of the uterus permits adequate evaluation.

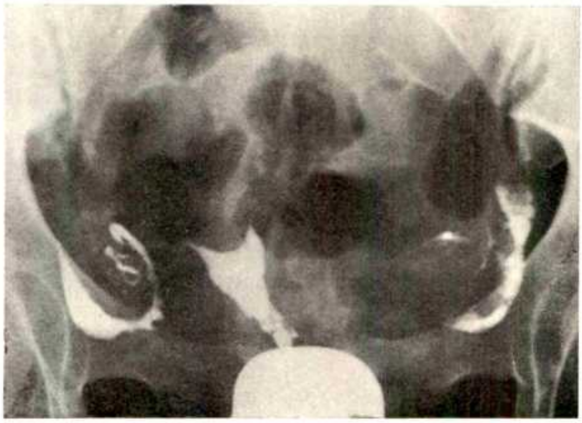


FIG. 24.
Hypoplastic and arcuate uterus. The isthmic narrowing is missing.

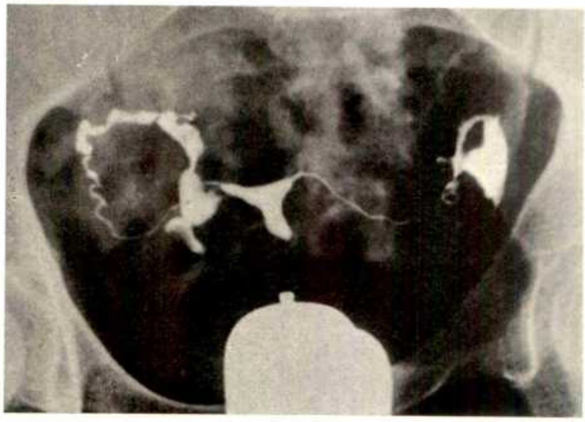


FIG. 26.
Star-shaped uterus. Three-point pattern through underdevelopment of the uterine body.

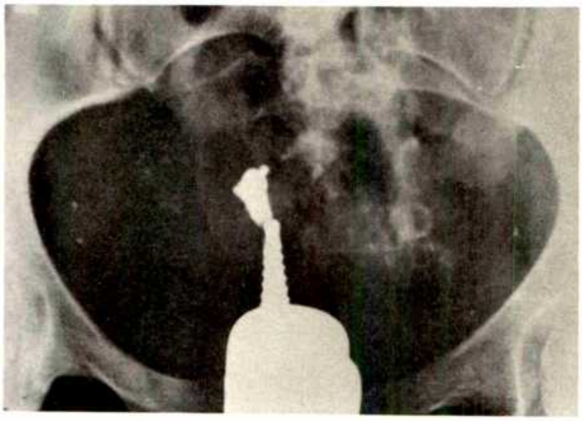


FIG. 25.
Pencil uterus. The uterine cavity is underdeveloped in width.

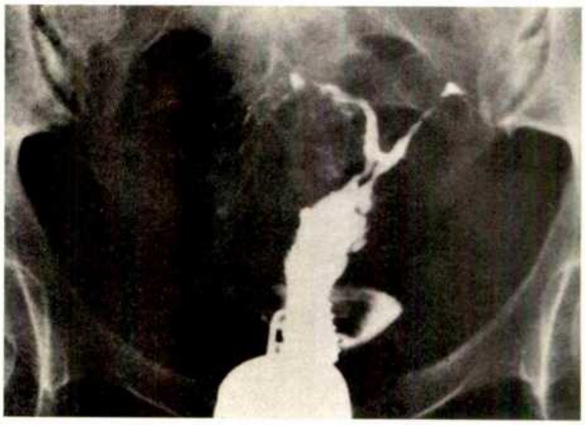


FIG. 27.
Complex malformation. The contrast medium was injected into the one ostium uteri. The single cervical canal is abnormally distended and elongated. A longitudinal septum is present in the isthmus. The uterine cavity is very underdeveloped and there is a marked saddle in the fundus.

The pattern of uterine hypoplasia varies according to the stage at which the growth of the organ was arrested.

Figure 23 typifies infantile uterus, a malformation due to very early arrest of uterine development. The cavity of the body is undersized, has not the usual triangular shape and is wider than normal with two distinct horns. The cervix is definitely elongated and dilated and out of proportion to the body. Another abnormality due to insufficient growth is gaping of the cervix and isthmus, *i.e.* incompetence of the internal uterine sphincter.

As will be noted also in Fig. 24, depicting a case of hypoplastic and arcuate uterus, the cervical canal continues into the cavity of the body without an isthmic constriction. This abnormality is highly important because it is one of the most frequent causes of spontaneous abortion.

Figure 25 illustrates another grade of uterine hypoplasia: pencil uterus, in which the organ develops in length but not in breadth and is anomalous in shape. The cavity takes the form of a very tapered triangle or even of a cylinder. As the figure shows, the anomaly is very often accompanied by lack of tubal patency.

Star-shaped uterus, illustrated in Fig. 26, is due to underdevelopment of the uterine body, which together with the two horns produce a three-pointed pattern.

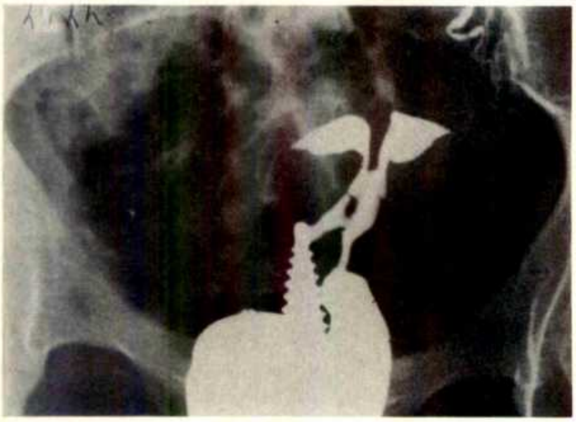


FIG. 28.

Complex malformation with a fistula opening into the left half of the vagina. Single cervical canal with duplication of the terminal portion. Filling defect in the middle portion of the canal. Slightly underdeveloped uterine cavity in anteversoflexion.

COMPLEX MALFORMATIONS

The malformations so far described fit into the proposed classification, but there are some multiple malformations so complex as to defy any classification.

The next two figures represent two cases of H-shaped uterus. In Fig. 27 the cervical canal is abnormally dilated and elongated; at the isthmus there is a filling defect attributable to the presence of a longitudinal septum, above which the cavities, markedly hypoplastic, are in communication. Fig. 28 shows a complex malformation combined with a fistula, which allowed the contrast medium to pass into the left side of the vagina.

CONCLUSIONS

Our findings stress the great value of hysterosalpingography in the study of congenital uterine malformations. Its diagnostic value coupled with the possibility in some cases of successful surgical correction are points which, together with considerable simplification of the method, have made for ever-increasing use of this type of investigation.

At one time almost confined to research into the causes of sterility, the investigation has widened its scope to include the pathology of pregnancy: repeated abortion, premature delivery and abnormal presentation may arise from uterine malformations of varying complexity.

Our material covers all the various stages of congenital malformations as well as transitional forms from one to another: from complete uterus didelphys to uterus bicornis bicollis and thence to septate uterus and to the complex malformations like H-shaped uterus, which, although characteristic in form, may be subdivided in that the H-shape may be due either to an isthmus between two completely divided cervices or to an isthmus between the two horns. If we turn to the less striking forms, where the malformation is confined to hypoplasia, all the complex mechanisms of hormonal, placental, ovarian and hypophysial dependence come into play. Co-existing malformations of the kidneys, ovaries and vagina may be present but hysterosalpingography may be diagnostic.

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The value of computerized axial tomography (CAT) in cranio-cerebral malformations

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ABSTRACT

Cranio-cerebral malformations commonly present in three ways: (1) with a visible structural defect; (2) with symptoms of neurological abnormalities but without evidence of raised intracranial pressure; (3) with macrocephaly or signs of raised intracranial pressure.

The large contribution made by computed axial tomography to the diagnosis and management of these cases is discussed in relation to a series of 217 patients. Invasive studies were performed in only 55 cases mainly to obtain further anatomical information prior to surgery.

Computerized axial tomography (CAT) has reduced the indications for other studies in paediatric neuroradiology to an even greater extent than in adult practice. This is partly due to the high incidence of cerebellar tumours in which, because of the uniformity of surgical approach, CAT evidence of a cystic or solid mass is sufficient for surgery, and partly because congenital and atropic conditions, which previously could only be diagnosed by invasive studies, can usually be elucidated sufficiently by CAT. In the latter group the precise diagnosis is frequently evident; in other cases sufficient information is obtained for management of the patient or for family counselling so that it is not ethically justifiable to proceed to invasive studies. There are, however, diagnostic limitations and conventional invasive procedures may be necessary to resolve these.

In an attempt to define more clearly the present contribution of CAT, and the indications for further neuroradiological studies in cranio-cerebral malformations, we considered that an analysis of a consecutive series of recent cases would be useful.

MATERIAL AND METHODS

We reviewed the clinical and radiological records of all cases of cranio-cerebral malformations, which have been submitted to CAT on the 160 matrix CT 1000 scanner at the National Hospitals for Nervous Diseases and the CT 1010 scanner at the Hospital for Sick Children up to June 30, 1977. We divided the patients into three clinical groups: Group 1—those with visible structural defects. Group 2—those presenting with various features suggesting a neurological abnormality without raised intracranial pressure. Group 3—those with signs of hydrocephalus or cranial enlargement.

RESULTS

There was a total of 217 patients with adequate plain scans. In 30% additional scans after intravenous contrast medium were obtained. General anaesthesia was used in only 10%.

Group 1

With visible structural defects. Malformations of the face and skull and certain systemic and cutaneous abnormalities occur as isolated features, but in several of them there is an increased incidence of abnormalities of the brain. Either lesion may be manifest when the other is latent and each may influence the treatment of the other. There were 111 such lesions requiring CAT to elucidate the possibility of associated intracranial malformations (Tables I–IV).

Additional studies, other than plain X-rays were usually unnecessary for diagnosis and invasive studies were performed only in 19 (17%) as indicated on the tables, usually to obtain anatomical information prior to surgery. Thus optic gliomas were examined by pneumoencephalography to show their precise relation to the chiasm if surgery was contemplated and acoustic neurinomas by vertebral angiography when the surgeon wished to know the adjacent vascular anatomy.

Group 2 (Table V)

Retardation, epilepsy, focal neurological deficit or microcephaly, alone or in combination, may be the clinical presenting features of a large number of congenital and acquired abnormalities. Although in some of these cases no lesion is evident on computed tomography, most of the congenital lesions can be recognized. These include severe deficiencies of cerebral substance, defects in commissural development and in neuronal migration, congenital tumours and hamartomatous masses and enzyme deficiencies. This group accounted for 20% of our congenital

TABLE I

Visible structural defects

Clinical features			CAT findings		Other studies
1. *Visible mass lesions*					
(i) Congenital tumours	Occipital dermoids	3	Posterior fossa masses	2	None
			Posterior fossa mass + abscess	1	None
	Nasal dermoid	1	Normal intracranial scan		None
	Orbital haemangioma	1	Typical orbital lesion Normal intracranial scan		None
(ii) Cranial encephaloceles or meningoceles	Posterior fossa	1	Hydrocephalus		None
	Parietal	3	Large cisterna magna extending through tentorium into meningocele + hydrocephalus (Fig. 1)	1	None
			Meningocele; otherwise normal	2	None
(iii) Spinal dysraphism		20	Dilated lateral and third ventricles	18	A.E.G. (1)
			Normal	2	
2. *Cranio-facial anomalies*					
(i) Medial facial clefts		2	Normal		None
(ii) Oro-facio-digital syndrome		1	Suprasellar arachnoid cyst + hydrocephalus		A.E.G.
(iii) Pierre Robin		1	Atrophy (dilated temporal horns)		None
(iv) Cornelia de Lange		1	Atrophy (dilated lateral and third ventricles)		None
(v) Conradies syndrome		1	Atrophy (generalized)		None
3. *Abnormalities of cranial growth*					
(i) Generalized disorder of bone growth					
	Achondroplasia	1	Communicating hydrocephalus		Pressure monitoring
	Osteopetrosis	2	Atrophy	1	None
			Normal	1	None
(ii) Premature fusion of sutures					
	Apert's syndrome	1	Hydrocephalus		A.E.G.
	Crouzon's syndrome	1	Hydrocephalus		None
	Trigoncephaly	1	Normal		None
	Saggittal/coronal	3	Normal		None
4. *Focal bone lesions*					
(i) Parietal cephalhaematona		2	Normal intracranial scan		None
(ii) Fibrous dysplasia		1	Normal intracranial scan		None
(iii) L. Temporo-parietal epidermoid		1	Expanded diploe, eroded inner table, compressed temporal lobe (Fig. 7)		Carotid
5. *Phacomatoses*					
(i) Sturge Weber		12	Table II		
(ii) Tuberous sclerosis		19	Table III		
(iii) Neurofibromatoses		29	Table IV		
(iv) Von Hippel-Lindau		3	Enhancing nodular tumours ± cysts in posterior fossa	3	Vertebral (3)
			Enhancing tumour + cyst in L. temporal lobe	1	Carotid

lesions presenting in infancy or early childhood. Most of them had a chronic history but in seven it was acute. Seven cases were part of a group of ten presenting with precocious puberty, without other clear cut clinical abnormality, being investigated for the possibility of hypothalamic tumours.

Studies other than plain films were performed in only 20 of these cases; air studies in 13, mainly in suprasellar lesions which had been revealed by CAT, in order to show the relationship to adjacent structures prior to surgery; angiograms in the five angiomatous malformations and in the venous angioma, the lipoma of the corpus callosum and the hydranencephaly.

Group 3 (Table VI)

Hydrocephalus, requiring investigation of the site and nature of the obstructing lesion, or macrocrania

TABLE II

Sturge Weber

Case no.	Age	Naevus	Plain skull Calcification	Plain skull Atrophy	CAT Calcification	CAT Atrophy
1	4	R & L	R & L	R & L	R & L	R & L
2	16	R	R	R	R (+ post. fossa)	R
3	12	L	L	L	L	L
4	13	L	L	L	L	L
5	7	R	R	R	R	Limited scan
6	10	R & L	R	R	R	R
7	9	R	R	R	R	R
8	10	L	—	L	L	L
9	16	R	R & L	R	R & L	R
10	8	L	R & L	L	R & L	L
11	2	L	—	L	L	L
12	1	R & L	—	L	L	L

TABLE III

Tuberous sclerosis

Case no.	Age	Diagnostic clinical features	Plain films	Other studies	CAT dense periventricular Nodules	Gliomas	Other lesions
1 a	3/12	—	—	—	—	—	L. Frontal Calcification (Fig. 9)
b	10/12	—	—	—	+	—	
2	8/12	—	—	—	+	—	—
3	9/12	—	—	—	+	—	—
4	11/12	+	—	(AEG+)	+	—	Atrophy
5	1 yr	+	—	—	+	—	—
6	15/12	+	—	—	+	—	—
7	21/12	+	—	—	+	—	—
8	2 yrs	+	—	—	+	—	—
9	4 yrs	+	C	—	+	—	—
10	4 yrs	+	—	—	+	—	Focal peripheral low attenuation (Fig. 11)
11	4 yrs	+	—	—	+	+	—
12	7 yrs	+	—	—	+	—	—
13	8 yrs	+	C	—	+	—	—
14	10 yrs	+	C	—	+	—	—
15	10 yrs	+	C P	—	+	+	—
16	14 yrs	+	C P	(AEG+)	+	+	—
17	14 yrs	+	C P	—	+	+	—
18	31 yrs	+	—	—	+	—	—
19	32 yrs	+	C P	(AEG+)	+	+ (Fig. 10)	—

C = calcification P = raised intracranial pressure

of other aetiology was the presenting feature in 62 of our cerebral malformations. Arachnoid cysts and aqueduct occlusion together accounted for 55% of these abnormalities and Dandy-Walker and Arnold-Chiari syndromes and aneurysms of the vein of Galen for most of the remainder. Further study by pneumoencephalography or angiography was performed in 27% of these cases.

Minor developmental variants, which are not of clinical importance but which need to be recognized to avoid confusion especially when they occur incidentally in association with significant pathology, include large fontanelles and parietal foramina which are confirmed by reference to the plain X rays, cavum septum pellucidum and vergae and coarctation of parts of the venticular system. These are observed not infrequently but their anatomy is as clearly shown on CAT as by pneumography and since they are not pathological they will not be discussed further.

TABLE IV

NEUROFIBROMATOSIS

Intracranial tumours				Other studies
Acoustic neuroma	4	Bilateral	2	Vertebral (4)
Optic glioma	5	Nerve alone	2	AEG (1)
		Nerve + chiasm	1	AEG (1)
		Nerve + chiasm + tract	2	None
Intracerebral glioma	4			None
Meningioma	1			Carotid
Hemihypertrophy	4			None
Deficiency of sphenoid wing	3			None
Ventricular dilatation and atrophy	8			None
Plexiform neurofibroma	2			None
Hypertrophy of choroid plexuses				None
Normal	3			None

TABLE V

		Total number of cases	Other studies
A. Retardation, spasticity, fits or focal neurological abnormality		323	
Congenital abnormalities		34	
Chronic presentation		27	
Agenesis of corpus callosum	10		A.E.G. (4)
Holoprosencephaly (with normal face)	1		None
Hydranencephaly	1		Ventric + Angio
Aicardi syndrome	3		A.E.G. (1)
Enzyme deficienceis and infiltrations	8		A.E.G. (1)
Hemisphere arachnoid cyst	2		None
Septo-optic dysplasia	1		A.E.G.
Venous angioma	1		Carotid Angiography
Acute presentation		7	
Angioma	5		Angiography (5)
Lipoma of corpus callosum	1		Angiography
Dermoid	1		None
B. Precocoius puberty		10	
Suprasellar arachnoid cyst	2		A.E.G. (2)
Optic/hypothalamic glioma	1		A.E.G.
Hamartoma	4		A.E.G. (1)
Normal	3		A.E.G. (1)

TABLE VI

HYDROCEPHALUS OR ENLARGED HEAD

Acute presentation			Other studies
Dandy-Walker	(2 with agenesis of corpus callosum)	3	None
Aqueduct Stenosis	(1 with agenesis of corpus callosum)	3	A.E.G. (2)
Arachnoid Cyst:	2 Suprasellar	9	None
	2 Behind third ventricle		A.E.G. (1)
	5 Posterior fossa		A.E.G. (4)
Chronic presentation			**Other studies**
Dandy-Walker		1	A.E.G.
Agenesis of corpus callosum + colpocephaly + heterotopia		1	None
Aqueduct Stenosis		9	A.E.G. (1)
Arachnoid Cyst:	4 Suprasellar	13	A.E.G. (1)
	1 Behind third ventricle		A.E.G.
	5 Posterior fossa		A.E.G. (3)
	3 Hemipshere		A.E.G. (1)
Aneurysm of vein of Galen		3	Angiogram (2)
Colpocephaly		1	None
Chiari malformation (without meningocele)		5	None
Megalencephaly		14	None

DISCUSSION

Group 1

Visible structural defects. CAT window levels should be adjusted to examine in turn the composition of the external abnormality, the bone adjacent to it and the brain.

Encephalocoeles and meningocoeles. Such herniations through developmental bony defects usually present as obvious masses on clinical study when they protrude subcutaneously, but basal lesions projecting towards the nose, sinuses, orbits or pharynx are not infrequently overlooked or misdiagnosed on clinical study. The bony defects may be shown on plain films but basal lesions especially are better defined by conventional tomography. These films are always reviewed in conjunction with the CAT.

Clinical management is influenced by (1) presence or absence of other cerebral abnormalities; (2) hydrocephalus, which should be treated prior to surgery on the lesion to decrease the likelihood of a cerebrospinal fluid fistula; (3) the extent and nature of the contents of the hernia and the relationships of adjacent structures.

CAT reveals most of these features (Fig. 1). Further information about the lesion itself may be obtained by computed tomography in the coronal axis of the lesion and in the plain of its neck, examining with varying window levels and widths to

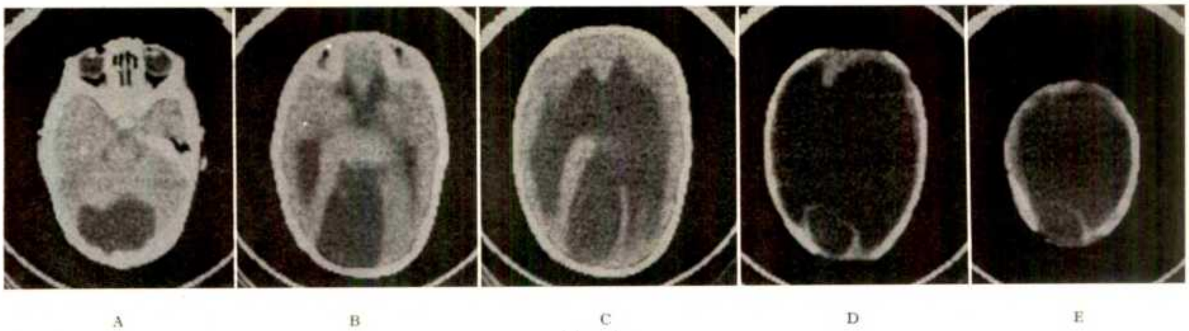


FIG. 1.

One year-old male. Enlarged head since birth with large, midline, parietal meningocele. CAT (A) just below tentorium, (B) (C) (D) and (E) progressively higher sections. There is an arachnoid cyst posterior to the cerebellum, passing through the tentorium, separating the occipital horns and extending into a midline parietal bone defect. There is gross hydrocephalus. In addition the anterior horns and bodies of the lateral ventricles are abnormal, with no evidence of a septum pellucidum, suggesting lobar holoprosencephaly.

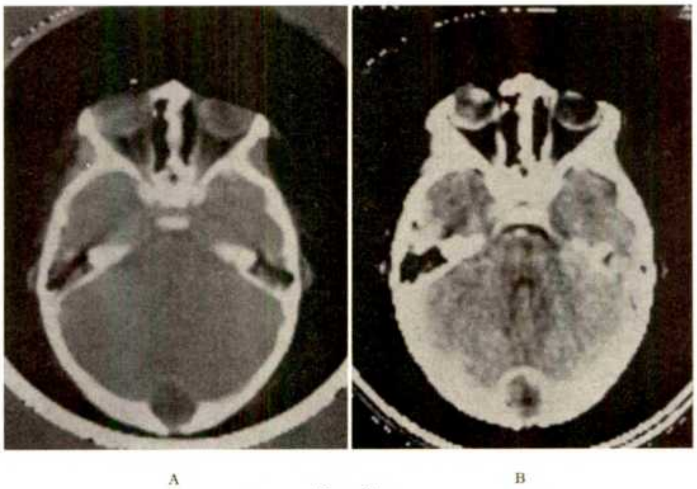


FIG. 2.

(A) Plain scan. (B) After intravenous contrast medium. There is a mass of diminished attenuation at the torcula which is associated with a marked excavation of the inner table and diploe and a small defect in the outer table. The transverse sinuses are displaced anteriorly by the mass which is typical of a dermoid cyst.

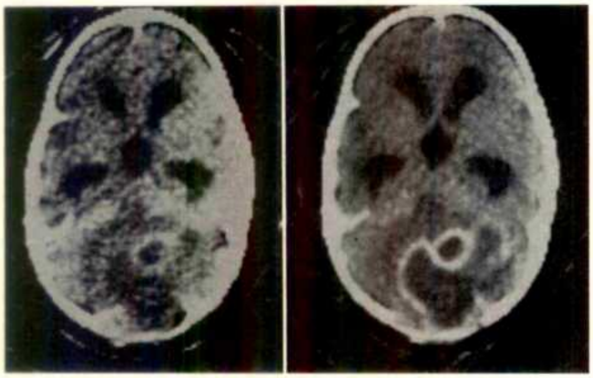


Fig. 3.

Abscess formation within posterior fossa dermoid. Scan (A) before and (B) after intravenous contrast medium. There are three low attenuation lesions with dense enhancing margins causing ring shadows in the position of the cerebellum with surrounding low attenuation. These were due to abscesses within the dermoid cyst. There is moderate hydrocephalus.

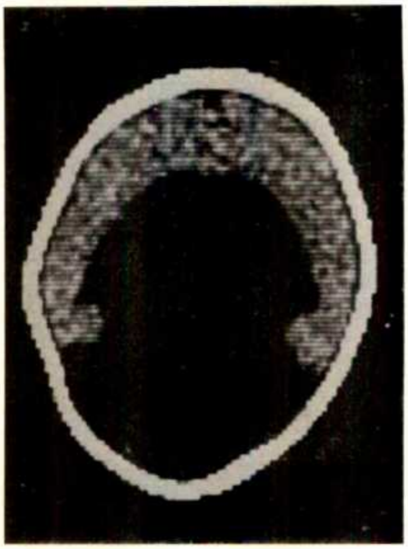


Fig. 4.

Holoprosencephaly. The interhemispheric fissure is absent and the cortex is continuous across the midline. There is no septum pellucidum and the single lateral ventricle is considerably dilated with a large posterior diverticulum.

show both the bone defect and the contents of the hernia. The latter may be difficult to assess due to partial volume effects and computer overshoot from adjacent bone in small lesions. Detailed anatomy of the major blood vessels and the relationship of optic pathways to basal meningocoeles can only be obtained from angiography and/or air studies, which may, therefore, be required for ideal presurgical planning (Pinto *et al*, 1975).

Dermoids, nasal gliomas and hamartomas. These lesions may have communicating superficial and intracranial components (Fig. 2). They are studied in the same way as the herniations. The attenuation coefficients in the lesion may indicate its nature; the size of the bony defect and the extent and relationships of the intracranial component are shown by CAT. Any hydrocephalus is evident; inflammatory complications, including abscess formation, within or near a dermoid may only be recognized after intravenous contrast injection (Fig. 3).

Spinal dysraphism. Overt spina bifida is associated with Arnold-Chiari, type 2, malformation in over 50% of cases, but this is an uncommon cause of obstruction to the outlet of the fourth ventricle. The hydrocephalus which occurs in over 90% of these cases (18 out of the 20 in our series) is most often due to aqueduct stenosis and, less frequently, to communicating hydrocephalus with obstruction in the ambient cisterns. Using the CT 1010 scanner the anatomy of the foramen magnum region may be shown and the absence of a cisterna magna suggests the probability of the Arnold-Chiari malformation. Enlarged caudate impressions and massa intermedia may also be evident, but it is usually not possible to recognize the depressed fourth ventricle and we have been unable to distinguish, without intrathecal Metrizamide, between elongated cerebellar tonsils closely applied to the upper cervical cord and inferior extension of the lower medulla, or to differentiate intraspinal extension of the fourth ventricle from hydromyelia. We still use myelography to show the anatomy around the foramen magnum region if the surgeon requires detailed information prior to local surgery on the lesion.

Holoprosencephaly. Development of the prosencephalic monovesicle is induced by the pre-chordal mesoderm behind the foregut which is the analogue of the medial facial structures (Mettler, 1947). Abnormal induction may cause holoprosencephaly associated with central facial anomalies, but either feature may occur in isolation. CAT is, therefore, indicated to reveal any intracranial lesion in such facial anomalies which include an obvious or minimal cleft, hypotelorism and trigonocephaly similar to that which occurs with metopic craniostenosis, but with a patent suture. The cerebral maldevelopment is not proportional to the facial deformity. The failure of differentiation of the prosencephalic vesicle into the hemispheres varies between retention of a holosphere, with a single ventricular cavity in the severe alobar cases (Fig. 4), to midline continuity of the frontal neo-cortex, combined with a defect in

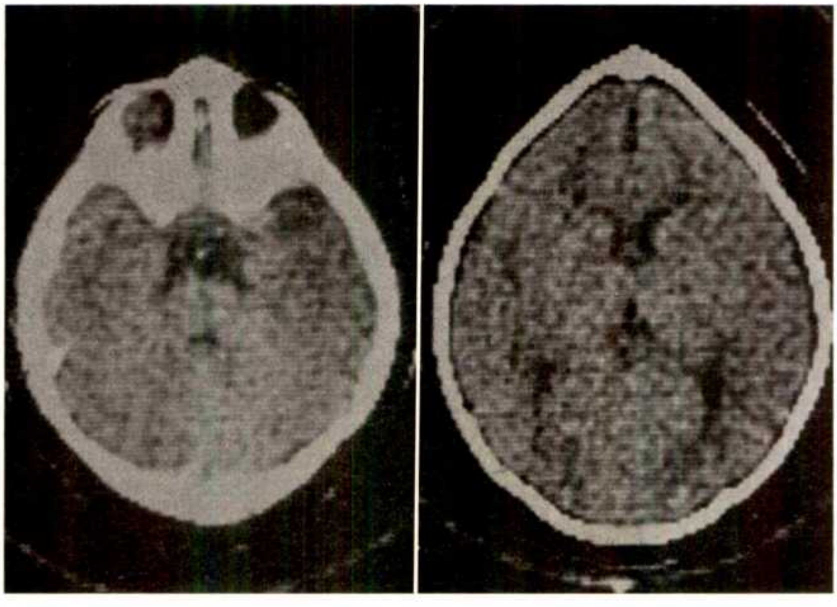


Fig. 5.

Trigonocephaly. The anterior frontal region is keel-shaped and there is thickening at the site of the prematurely fused metopic suture. (A) There is hypotelorism. (B) The brain is normal.

the septum pellucidum and agenesis of the corpus callosum in lobar holoprosencephaly (Kurlander *et al.*, 1966).

Frequently a thin-walled dorsal extension of the monovesicle replaces the posterior parts of the cerebrum. Microcephaly is usually present, but sometimes the dorsal sac may be large and cause macrocrania. In such cases the cerebral mantle may rotate posteriorly, leaving a large extracerebral space anteriorly. This may superficially resemble hydranencephaly or bilateral subdural effusion, but the additional features of holoprosencephaly will distinguish these. In holoprosencephaly the falx is characteristically absent; though occasionally a hypoplastic one develops posteriorly. Absence of the falx may be useful when the diagnosis is in doubt since it does not occur in other conditions.

Cranial Growth Abnormalities. Fusion of sutures can be shown in the various forms of craniostenosis (Fig. 5). The small volume of the orbits is evident in cases with proptosis as is the presence and degree of hypertelorism or hypotelorism. Communicating hydrocephalus is an occasional association which may alter management.

The large vault of achondroplasia may be due to disordered bone growth associated with the hypoplastic base, but there may be communicating hydrocephalus (James *et al.*, 1972).

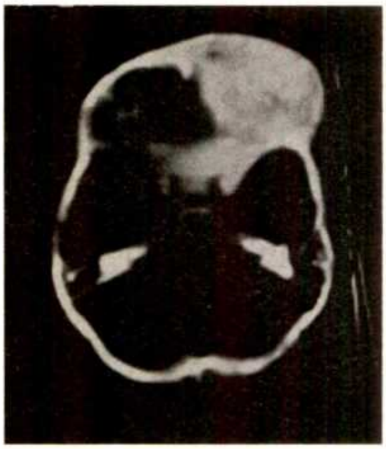


Fig. 6.

Fibrous dysplasia. There is expansion of the diploe in the convexity and orbital plate of the right frontal bone and in the pre-sphenoid. The expanded bone is of irregular density, typical of fibrous dysplasia.

Deformity of the vault may be due to periosteal bone formation as, for example, over a cephalhaematoma, to abnormally thick diploe with increased calcification within it in fibrous dysplasia (Fig. 6), or low attenuation within it in intradiploic epidermoids (Fig. 7).

Our case of Klippel-Trelawney-Weber syndrome was associated with hemihypertrophy involving all tissues.

Most of the intracranial manifestations of phakomatoses can be recognized at an earlier stage by CAT than by other neuroradiological studies, which should, in general, be held back until specifically indicated as, for example, to elucidate vascular anatomy adjacent to a neurofibroma or haemangioblastoma prior to surgery, or to detect lesions of the blood vessels themselves in neurofibromatosis or von Hippel-Lindau syndrome.

Sturge-Weber syndrome. Our 12 cases ranged from two to 16 years (average 8.6) and at the time of CAT the typical naevus was apparent. Plain skull films showed evidence of hemiatrophy or microcephaly in all our cases; enlargement of the ipsilateral hemicranium as described by Enzmann *et al.* (1977) was not seen. Diagnostic superficial calcification was present on plain X rays in nine of our cases; the other three were aged one, two and ten years respectively. CAT showed calcification and ipsilateral atrophy in all cases and the changes were always more extensive than on the plain films. In two cases the facial naevous was bilateral; in one of these the radiological changes were bilateral, but in the other they were unilateral. In two others with unilateral naevus the calcification was bilateral. In the oldest patient there was calcification adjacent to the cerebellar cortex on both sides in addition to typical unilateral cerebral calcification. Thus the cerebral changes are not necessarily confined to the side of the naevus and may involve the cerebellum also.

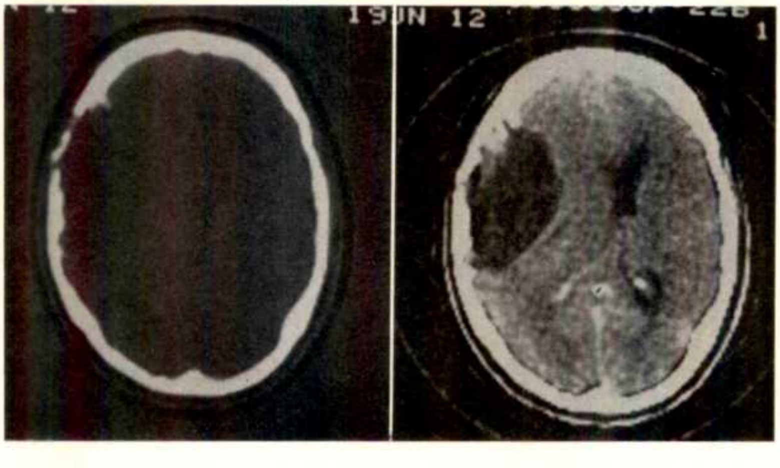
Intravenous contrast medium was given in only one case and caused diffuse superficial enhancement on the side of the calcification (Fig. 8). Enzmann *et al.* (1977) gave contrast medium to two cases; one showed marked and the other slight superficial enhancement. Linear densities, suggesting enlarged deep veins, which are a well recognized feature of this pathology, were also evident in one case.

Tuberose sclerosis (Epiloia). Our 19 cases ranged from three months to 32 years, but only two cases were over 14 years. Clinical features of the disease were evident in 16 cases and one other had a strong family history. In three cases the CAT findings were the first indication of the diagnosis.

Plain X-rays showed typical calcification in seven cases and in four of these there was also evidence of raised intracranial pressure.

CAT showed typical subependymal, partially calcified nodules in 18 cases at the time of presentation. In the other case, aged three months, there was irregular amorphous calcification deep in the left frontal lobe; a repeat scan at the age of ten months showed typical subependymal nodules (Fig. 9).

Large masses adjacent to the foramina of Monro, typical of the gliomata occurring in this syndrome



A B

Fig. 7.

Epidermoid. (A) Plain scans (L 100 W 400). The medial surface of the temporal bone is eroded and the erosion has extended through to the outer table anteriorly. The inner table is elevated at the margins of the lesion. (B) Same cut after intravenous contrast medium (L 18 W 40). The mass is of low attenuation (attenuation +5) and there is no enhancement within it. There is a little enhancement around its medial border. It is causing considerable mass effect as shown by compression of the left lateral ventricle and deviation of the midline towards the right side.

(Kapp *et al.*, 1967) were shown in five cases, in all of which there was obstructive hydrocephalus due to these tumours (Fig. 10).

Low attenuation lesions which did not enhance, presumably due to cortical tubers, in addition to typical subependymal nodules, were present in one case (Fig. 11). There was unilateral atrophy in another case. Arterial lesions are known to occur in tuberous sclerosis (Hilal *et al.*, 1971) and it is possible that the atrophy was due to either ischaemia or to dysgenesis. Although pneumoencephalography was performed in three early cases in our series, the CAT findings are usually so specific that no other procedure is indicated.

Neurofibromatosis. Our 29 cases showed most of the cranial manifestations of the syndrome.

Ten presented with orbital problems which were resolved by CAT and plain X-rays. Enlargement of the optic nerves and chiasm due to glioma may be difficult to assess in asymmetrical orbits unless overlapping cuts in the axis of the optic nerves are obtained. The numerous lesions causing proptosis

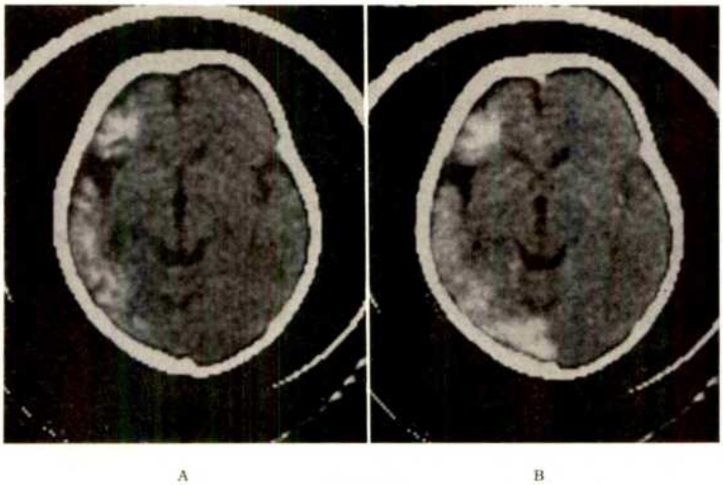


FIG. 8.

Sturge-Weber syndrome. (A) Plain scan. There is typical subcortical calcification throughout most of the left hemisphere. There is left hemiatrophy with diminished cerebral substance on the left side, widening of the left subrachnoid space and thickening of the cranial vault. (B) Same cut after intravenous contrast medium. There is enhancement of the brain adjacent to the calcification but extending beyond it to the occipital pole.

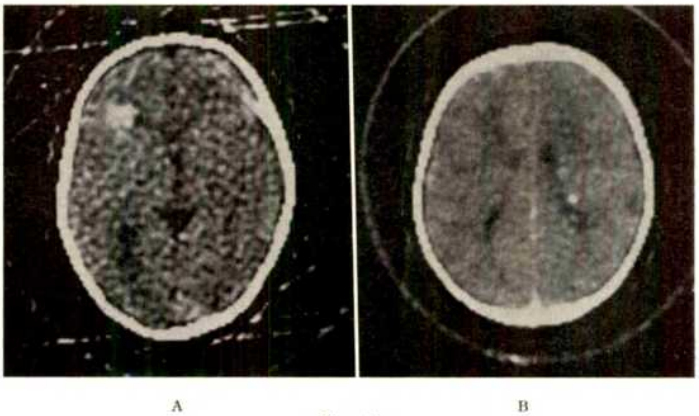


FIG. 9.

Tuberous sclerosis. (A) Aet 3/12, plain scan. There is amorphous calcification in the white matter of the left frontal lobe. (B) Aet 10/12 after contrast medium. Typical subependymal nodules are now evident. They were present on plain scan but more apparent after enhancement.

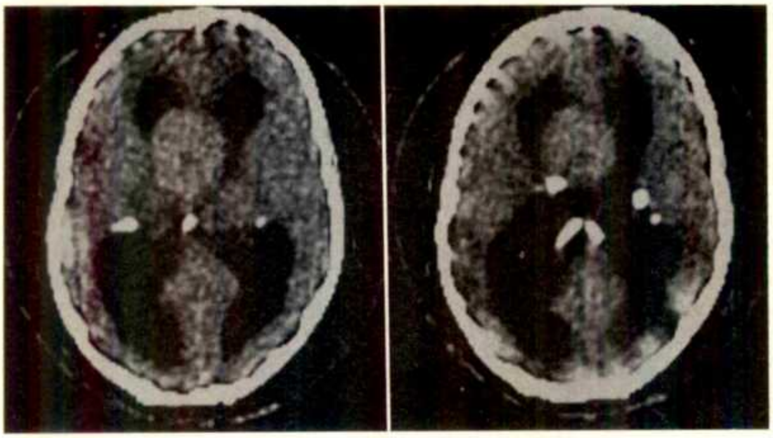


Fig. 10.

Tuberous sclerosis. CAT adjacent cuts with lower one at level of foramina of Monro. Four typical calcified subependymal nodules are shown. There is a large mass of brain attenuation encroaching into both frontal horns from the region of the foramina of Monro which is typical of the gliomata occurring in tuberous sclerosis. The lateral ventricles are dilated and the tips of two shunt tubes (arrow) are shown in the bodies of the lateral ventricles.

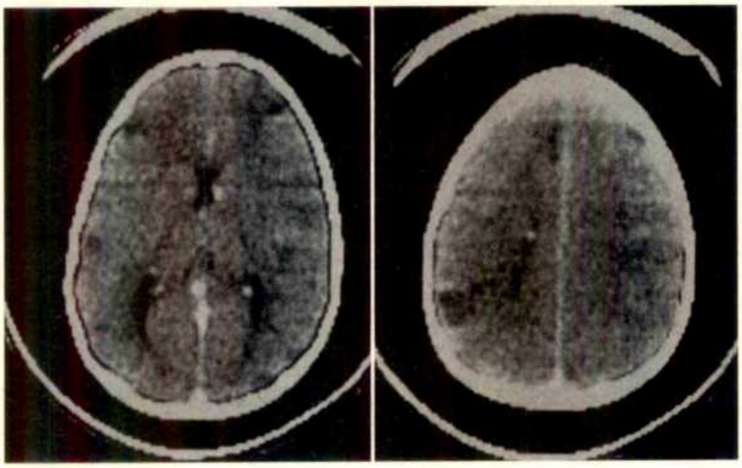


Fig. 11.

Tuberous sclerosis. Sections taken 1 cm apart after intravenous contrast medium. Typical partly calcified subependymal nodules are shown. In addition there are low attenuation lesions, presumably tubers, in the cortical regions of both hemispheres.

are simply resolved by CAT and exclusion of tumour by this means has saved further investigation and exploratory surgery (Fig. 12).

Intracranial tumours, not infrequently multiple (Roderigues and Morgan, 1966) are best diagnosed and followed-up by CAT (Fig. 13). The internal auditory meatuses cannot be adequately examined by CAT alone and, when intracanalicular tumours are suspected, other studies may be indicated.

Unilateral ventricular enlargement occurred in eight cases. This may be associated with hemihypertrophy (three cases), but the cause was not evident in five cases (Fig. 14). Arterial involvement by the disease is one possibility. The cause of macrocranium, which is frequently present in neurofibromatosis (Holt and Kuhns, 1976) is best elucidated in individual cases by CAT. It was present in our four patients with hemihypertrophy and in one other

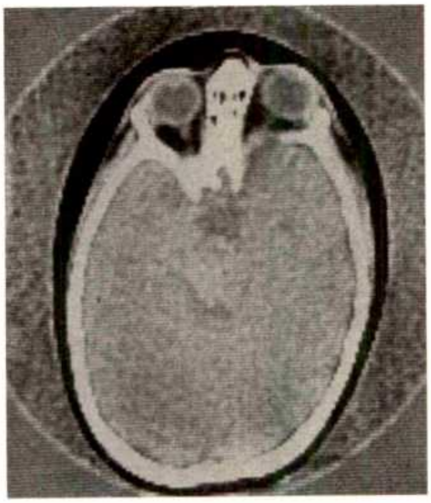


FIG. 12

Neurofibromatosis, presenting with right proptosis. There is dysplasia of the right greater wing of sphenoid with bulging of the temporal lobe into the posterior part of the orbit, which is the cause of the proptosis. No intraorbital lesion or further abnormality was shown.

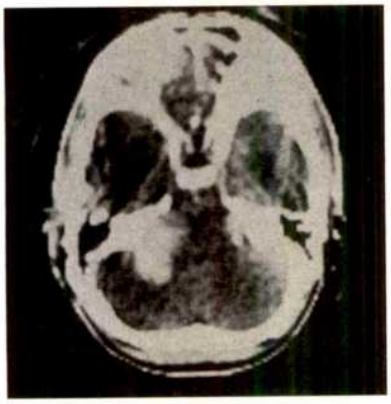


FIG. 13.

Neurofibromatosis, bilateral acoustic neurinomata. Scan after intravenous contrast medium. This large, left-sided tumour and small right-sided tunour were best demonstrated at a relatively high window level (L 35, W 50) at which the cerebral substance is not well shown.

with megaloencephaly associated with a cerebral glioma.

CAT has been used in the phakomatoses as a screening procedure. We have observed, however, that despite careful CAT with enhancement, some small non-cystic haemangioblastomas were not demonstrated, at a time when they were visualized by angiography.

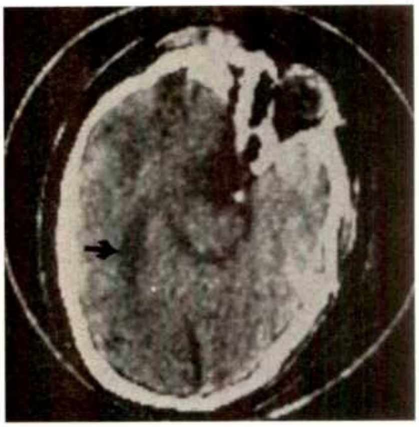


FIG. 14.

Neurofibromatosis, hemi-hypertrophy. There is enlargement of the left temporal lobe associated with expansion of the left hemi-cranium. The left lateral ventricle is dilated (left temporal horn →). There is a plexiform neurofibroma of the left side of the face.

Group 2

An analysis of the large number of conditions which presented in our second group is given in Table IV. CAT is the only radiological investigation capable of showing some of these conditions and the most appropriate first study in most of them.

Enzyme deficiences may be recognized by systemic changes, but when their effects are confined to the central nervous system CAT may raise this diagnostic possibility. CAT is useful in the former group to show the extent of intracranial involvement as, for example, in mucopolysaccharsidoses in which cerebral infiltration may be revealed as diffuse white matter low attenuation, or focal masses and there may be arachnoid cyst formation or hydrocephalus, any of which may be associated with macrocephaly. Cerebral infiltration was shown in lipoidoses (Fig. 15) and calification in the basal ganglia in carnitine deficiency.

In the group confined to the nervous system, paraventricular low attenuation due to white matter degeneration or hypoplasia may occur, sometimes associated with atrophy, or atrophy may be the only recognizable feature. We have seen such changes in metachromatic, Krabbe's (Fig. 16) and adrenoleukodystrophies (Kendall *et al.*, 1977) in dihydrofolate reductase deficiency and Leigh's disease.

Dysgenesis of the commissural plate. In total agenesis of the corpus callosum there is separation of the lateral ventricles so that their medial walls do not oppose at any point. The third ventricle extends up between them and is often wide, particularly its posterior part. The medial borders of the lateral

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ventricles are straight or concave medially, with slit-like dorsal extensions of the cella media (Fig. 17). In uncomplicated cases the anterior horns are narrow relative to the trigonal and posterior temporal regions, which are moderately dilated due to failure of development of the posterior fornices, and to colpocephaly due to hypoplasia of white matter (Fig. 18) (Probst, 1973). These cases are more prone than normal children to perinatal anoxia which may cause encephaloclasis; this tends to be more marked in the trigonal and temporal regions, resulting in further dilatation. There is frequently microcrania with patent sutures which may be the presenting feature; macrocrania occurs in about 20% of cases, usually associated with dilated ventricles, a cystic suprapineal recess or accompanying lesions such as interhemispheric cysts or lipoma of the corpus callosum (Brun and Probst, 1973). Callosal dysgenesis is also found in association with Dandy-Walker syndrome and Aicardi's syndrome.

In lesser degrees of dysgenesis the anterior parts of the lateral ventricles are normal but it is possible to diagnose the condition if the third ventricle extends between the separated posterior parts of the bodies, especially when there is also dilatation of the trigonal regions. The cardinal CAT sign of agenesis, however, is separation of the medial walls of the ventricles; if this is not present an absolute diagnosis

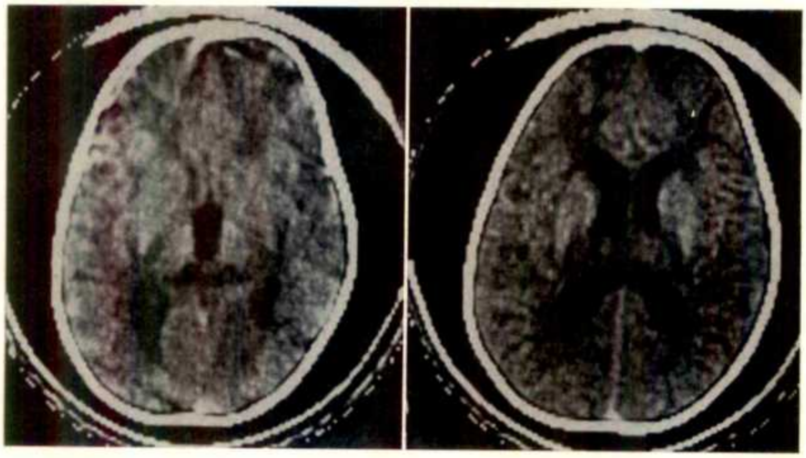


Fig. 15.

Tay-Sach's disease. There is macrocephaly associated with infiltration of white matter which is of diminished attenuation. The lateral and third ventricles themselves are normal.

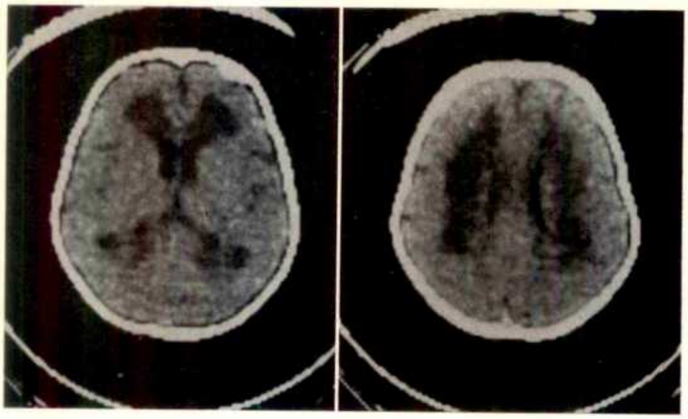


Fig. 16.

Krabbe's leukodystrophy. Well defined, symmetrical, periventricular low attenuation typical of the leukodystrophies is shown. The lateral ventricles themselves are normal.

is not possible without an air study. In this series there are no cases in which agenesis was shown by encephalography but not recognized on CAT.

Defective neuronal migration. Dysgenesis of the corpus callosum is frequently associated with other defects of neuronal migration causing colpocephaly and/or heterotopia of grey matter (Fig. 18). The latter is recognized by subependymal nodules (Bergeron, 1967) of similar attenuation to brain tissue, causing irregularity of outline of the lateral ventricles; the third and fourth ventricles are not affected.

Nodular ectopia and colpocephaly occur with lissencephaly (Wesenberg *et al.*, 1966) in which there is hypoplasia of white matter and failure of development of the cerebral cortex; calcification of unknown origin has been shown to occur in the upper margin of the septum pellucidum in this condition.

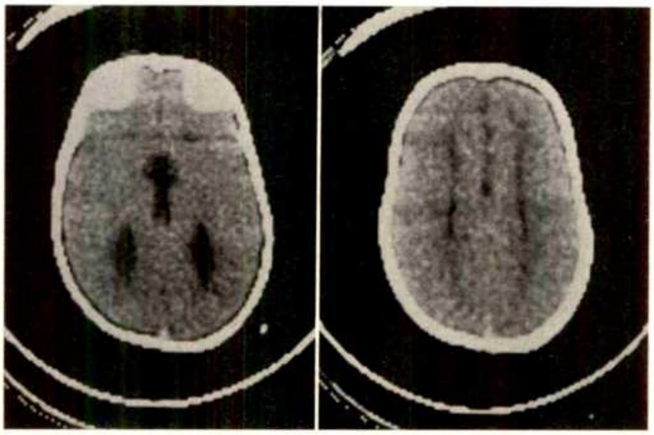
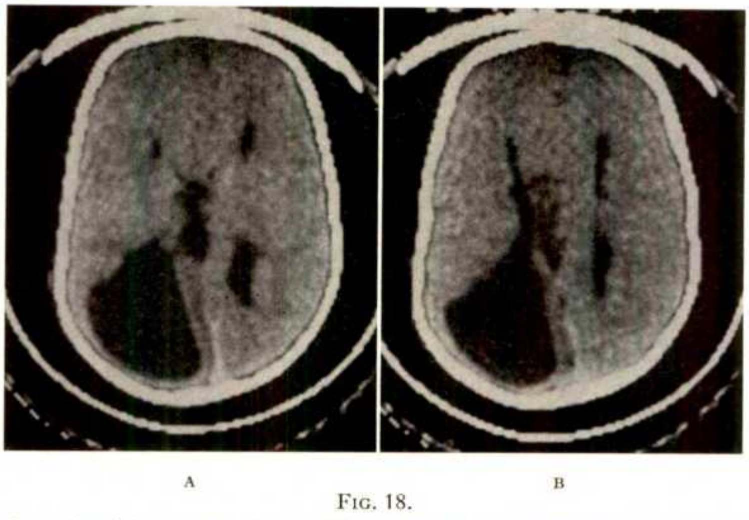


FIG. 17.

Simple agenesis of the corpus callosum. The lateral ventricles are separated. The third ventricle extends up between them. The anterior horns and bodies of the lateral ventricles are small. The trigonal regions are slightly larger. There is slight irregularity of the contours of the bodies of the lateral ventricles, probably due to hetertopia of grey matter.



A B

FIG. 18.

Agenesis of the corpus callosum. The lateral ventricles are separated and the third ventricle extends up between them with elongation of the foramina of Monro. The lateral ventricles are narrow and the margins are irregular due to nodules of heterotopic grey matter. The left trigone and occipital horn are dilated due to hypoplasia of the adjacent white matter (colpocephaly).

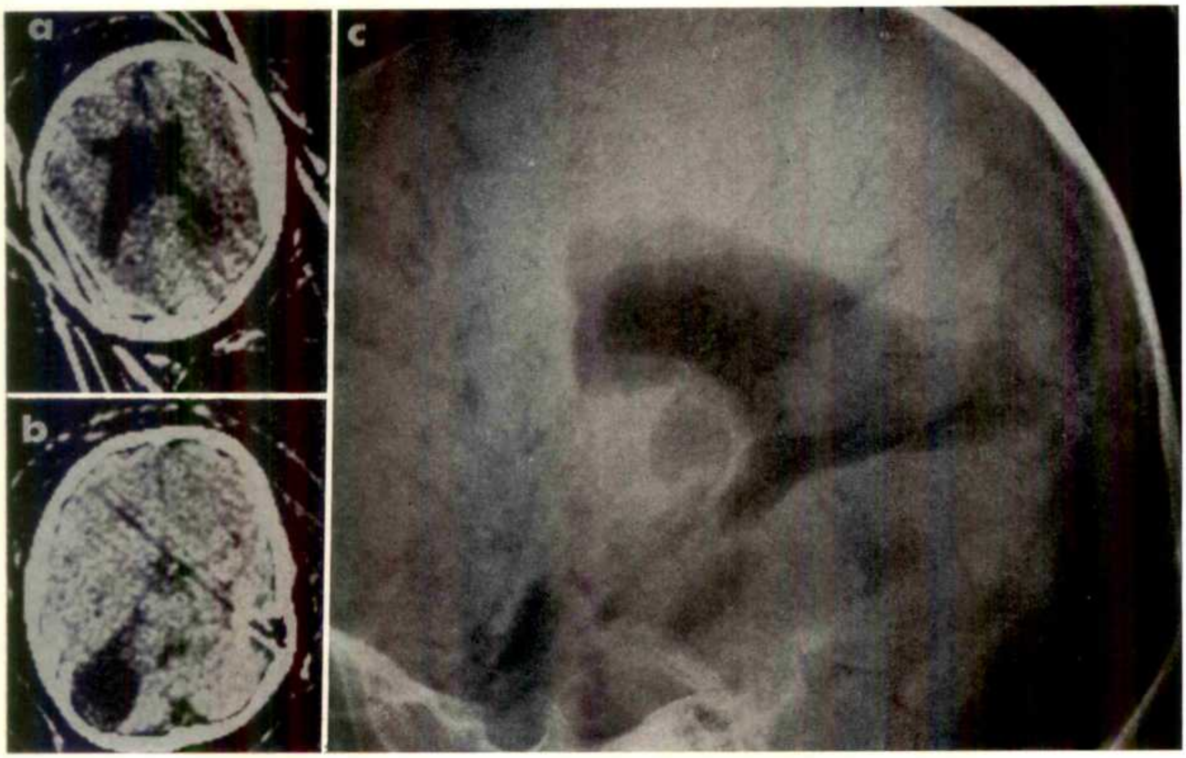


FIG. 19.

Aicardi's syndrome. (a) The walls of the lateral ventricles, especially of the right, are irregular due to the presence of heterotopic nodules of grey matter. (b) There is an arachnoid cyst adjacent to the left petrous bone and cerebellar convexity associated with hypoplasia of the left cerebellar hemisphere and some expansion of the left side of the posterior fossa. (c) Pneumoencephalogram. Brow-down lateral projections. A large nodule of heterotopic grey matter is shown projecting from the roof of the right occipital horn into the trigone. The lateral ventricles are moderately dilated.

Nodular ectopia is also a feature of Aicardi's syndrome (Fig. 19) and occasionally it is recognized as an isolated abnormality.

Septo-optic dysplasia. Absence of the septum, as distinct from secondary rupture, is associated with a straight configuration of the posterior margin of the rostrum of the corpus callosum due to lack of deviation which occurs towards a normal septum (Fig. 20). The anterior part of the third ventricle may be wide, but is usually normal on CAT which does not reveal the minor changes in its anterior recesses. In addition, the small optic foramina could be shown at appropriate window settings, but it is not possible to measure the size of the optic nerves due to partial volume effects. The diagnosis of this condition is essentially clinical and the role of CAT is supportive and to exclude further abnormalities. It is not necessary to proceed to invasive studies.

Porencephaly may follow encephalomalacia of any aetiology but in one variety (schitzencephaly), which

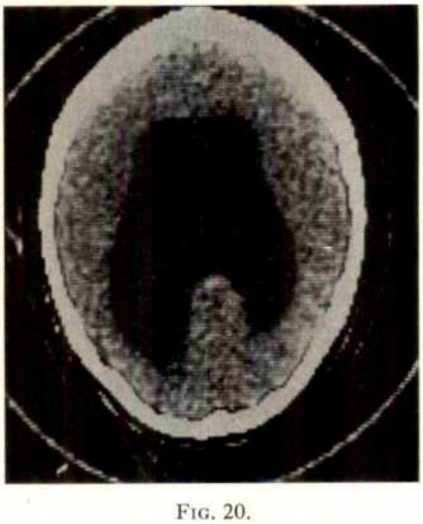
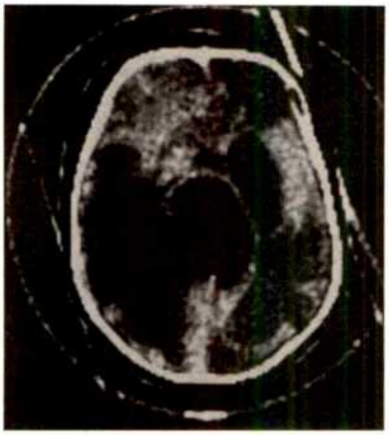


FIG. 20.

Septo-optic dysplasia. The septum pellucidum is absent. Note the horizontal configuration of the rostrum of the corpus callosum.



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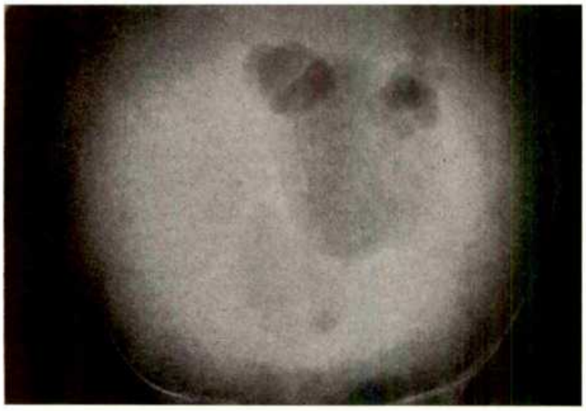

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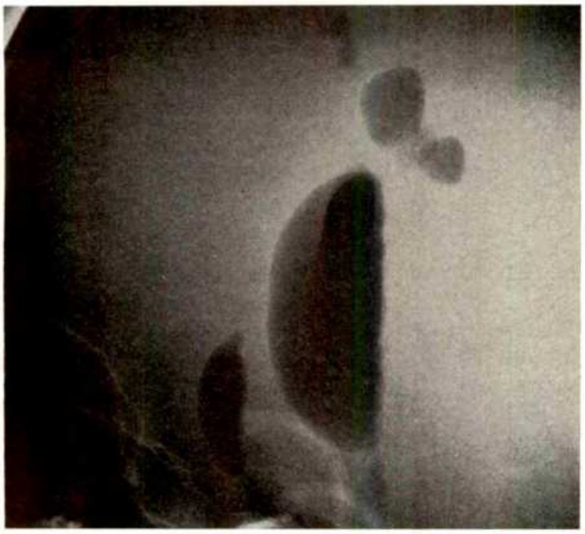

C

is initiated relatively early in cerebral development, the cavities are usually large in a malformed brain (Yakovlev and Wadsworth, 1946a, 1946b). The condition tends to be most marked in the Rolandic region and, when severe, may extend from ependyma to pia. When the cysts do not communicate freely with cerebrospinal fluid spaces they are shown as avascular masses on conventional contrast studies. The cysts are frequently associated with hemiatrophy though there may be focal mass effect or macrocephaly. All these abnormalities are evident on CAT, the cysts appearing as sharply defined masses of water attenuation (Fig. 21A), without any enhancement after intravenous contrast medium. Intrathecal Metrizamide with repeated CAT, or air encephalography or cystography is necessary (1) to determine if connections are present between multiple cysts and between cysts and the ventricles or subarachnoid space prior to drainage procedures (Fig. 21B); (2) to distinguish the lateral ventricles from the cysts when this is not possible on plain scans.

In *hydranencephaly* the posterior fossa, corpus striatum and cerebral substance in the temporal and inferior parts of the frontal lobes are present and are shown at standard window levels (Fig. 22A). The falx, projecting into the upper part of the fluid-filled cranium, is best shown with a wide window; its presence may be helpful in excluding holoprosencephaly with a cyst over-riding the cerebral mantle. Very thinned cerebral substance occurring in gross hydrocephalus may not be evident with standard window settings and should be searched for at different window levels to avoid mistaking this condition for hydranencephaly. Coronal cuts may possibly be necessary to exclude large subdural hygromas compressing the cerebral substance inferiorly (Harwood-Nash, 1977) but we have not seen such a case. Cerebral angiography is rarely necessary for confirmation of the diagnosis (Fig. 22B).

Group 3

In our congenital defects presenting with raised intracranial pressure, hydrocephalus or enlarged

FIG. 21.

(A) Schitzencephaly with multiple porencephalic cysts. There are multiple well defined regions of the same attenuation as cerebro-spinal fluid. The lateral ventricles are difficult to distinguish from these regions with certainty, but they are probably dilated and displaced towards the right side.

(B and C) Since the head had enlarged, air was introduced into a left-sided cyst. After manipulation of the head air has partially outlined the dilated lateral ventricles and several of the cysts. This indicates that a considerable part and possibly the whole of the obstructed system can be drained by a single shunt procedure.

head (Table V), CAT was again the most important initial study. Occlusion of the ventricular system is recognized by dilatation of the part above the obstruction. The c.s.f. pathways below the level of the occluding lesion are usually normal or small, but they may be dilated due to obstruction of the subarachnoid space at the level of the tentorium, caused by brain herniation, or around the expanded hemispheres due to compression or incomplete development of the space. In simple occlusion there is no tumour mass, abnormal attenuation or enhancement after intravenous contrast medium, which is given in these cases unless invasive studies are specifically indicated.

The distended system bulges towards the site of obstruction especially when membranous, but a tomogram along the axis of the occluded part of the ventricular system would be necessary to reveal this. In simple aqueduct stenosis there is usually marked dilatation of the third ventricle, with ballooning of the posterior recesses and often of the mouth of the aqueduct. The quadrigeminal cistern, which is splayed by downwards pressure of the dilated third ventricle, outlines the symmetrical midbrain (Fig. 23). The actual occlusion in the aqueduct itself is not shown by CAT but inferred from the indirect evidence. Masses at the posterior end of the third ventricle and in the brainstem are usually visible due to deformation of the adjacent structures on unenhanced scans (Fig. 24) but contrast medium is valuable in confirming small gliomas (Fig. 25) and angiomatous malformations.

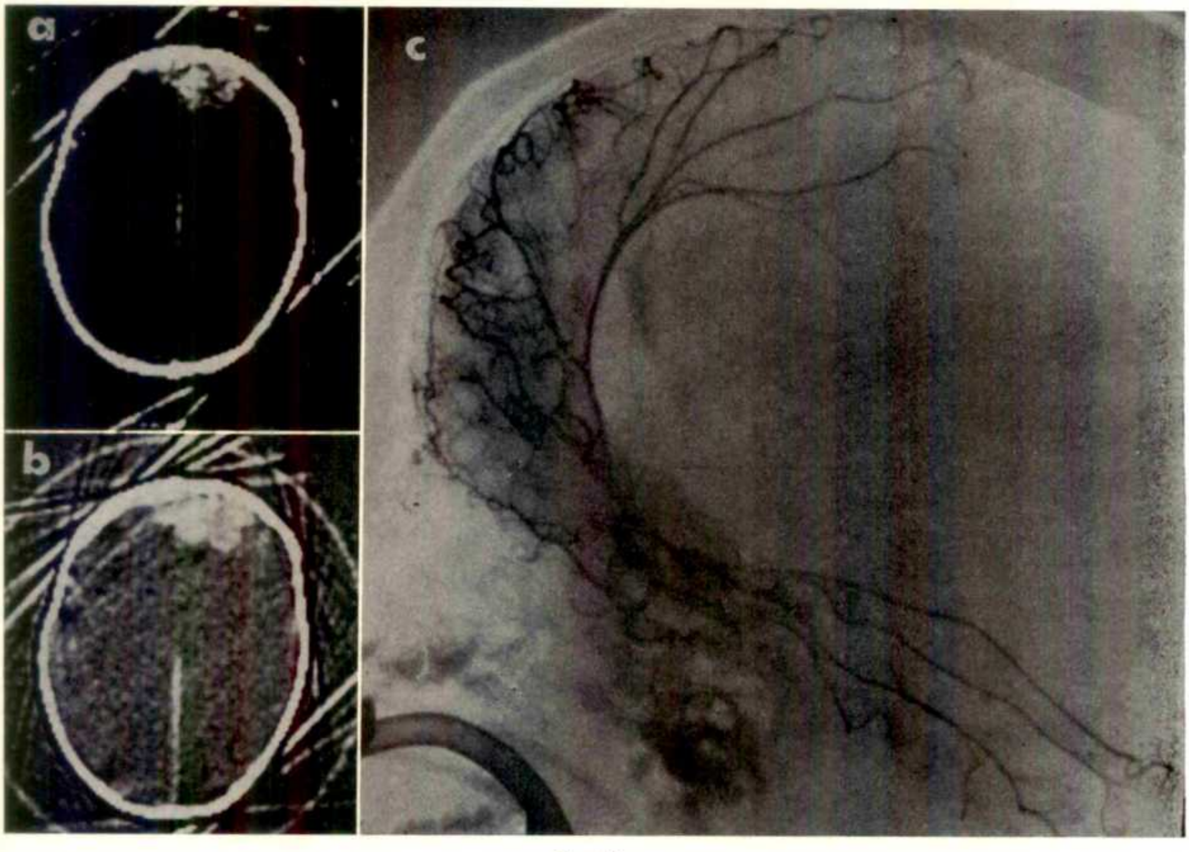

Fig. 22.

Hydranencephaly. (a) A small nodule of cerebral tissue is present in both frontal regions. The remainder of the cranial cavity at the level of section is filled with cerebro-spinal fluid. The falx is visible at usual window levels (L, 18, W 40 EMI units) but is better seen with a low window level (b) (L 10, W 40) with which the cerebrospinal fluid appears relatively dense. Note computer artefact due to poorly fitting water bag. (c) Subtraction film of lateral projection of right carotid angiogram. Capillary circulation is shown in brain substance in the medial frontal supplied by the anterior cerebral artery and in the temporal lobe supplied by the posterior cerebral artery. The middle cerebral artery is hypoplastic and most of its branches are absent. The remainder of the cerebral substance is deficient.

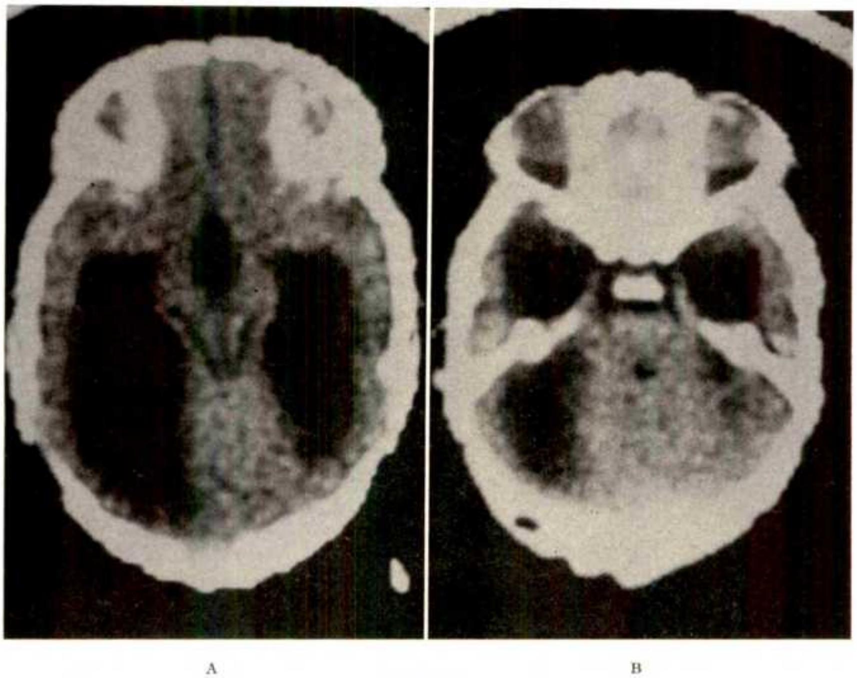

FIG. 23.

Aqueduct stenosis. Unenhanced scan. (A) at level of third ventricle. The lateral and third ventricles are markedly dilated but not deformed. The cisterns in the tentorial hiatus appear slightly compressed from the lateral aspects but are otherwise normal and there is no indication of any mass. (B) Through posterior fossa. The fourth ventricle and basal cisterns are normal.

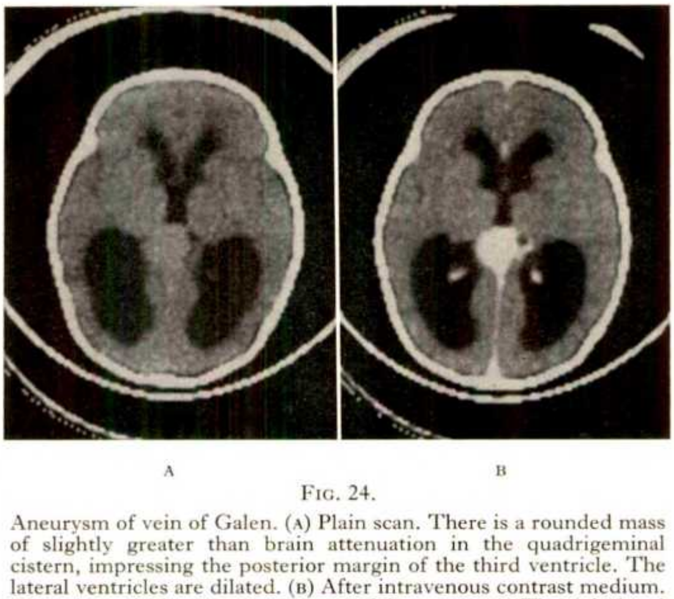

FIG. 24.

Aneurysm of vein of Galen. (A) Plain scan. There is a rounded mass of slightly greater than brain attenuation in the quadrigeminal cistern, impressing the posterior margin of the third ventricle. The lateral ventricles are dilated. (B) After intravenous contrast medium. There is marked even enhancement of the aneurysm. The right basal vein and the straight sinus are shown in continuity with it.

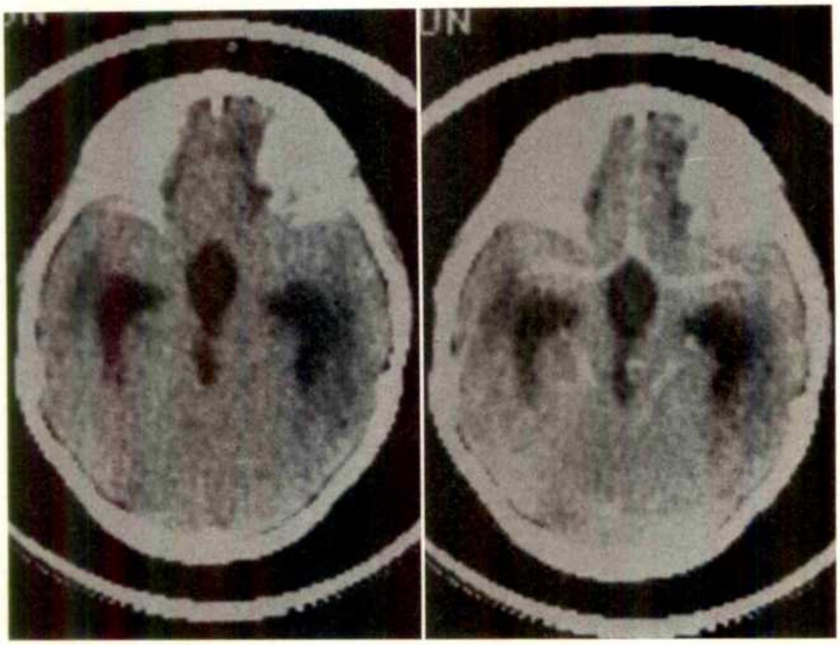

Fig. 25.

(A) Tumour at posterior border of the third ventricle causing obstruction. There is symmetrical dilatation of the lateral ventricles with periventricular low attenuation. The third ventricle is dilated and a small mass encroaches into its posterior part from the right side. (B) After intravenous contrast medium there is a little enhancement within the mass.

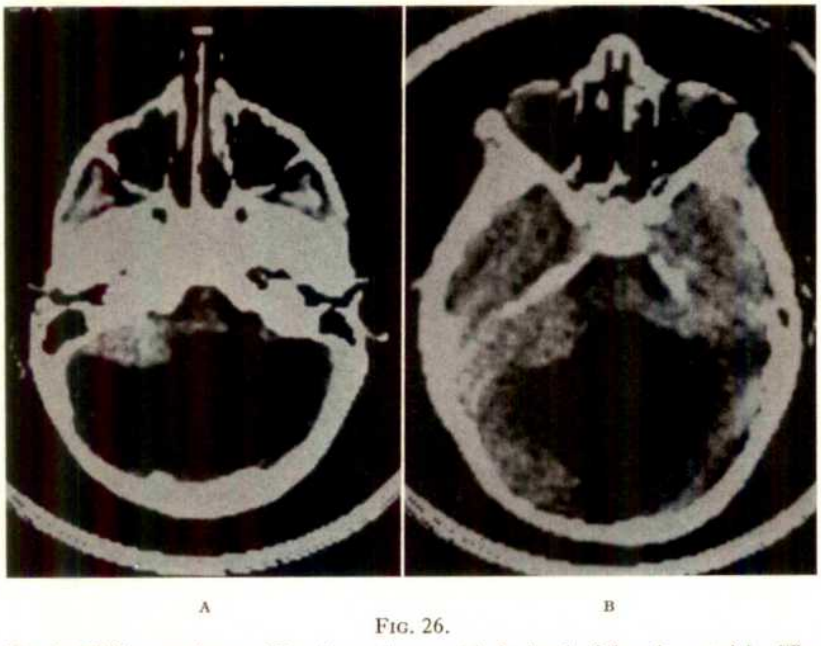

Fig. 26.

Dandy-Walker syndrome. Unenhanced scan. (A) At level of fourth ventricle. The cerebellum is hypoplastic, only a small amount of the right hemisphere and a little more of the left hemisphere are visible. (B) A large space of cerebro-spinal fluid attenuation fills most of the posterior fossa and extends up to the tentorium.

Obstruction in the fourth ventricle or at its outlet usually causes enlargement of the ventricle but sometimes this is of lesser degree than that of the supratentorial ventricles, in which case diagnosis of the site of obstruction may not be possible without other studies. When hydrocephalus is accompanied by marked enlargement of the fourth ventricle the distinction between simple obstruction, arachnoid cyst and Dandy-Walker syndrome is of some importance because, in the former, simple drainage of a lateral ventricle will reduce the pressure throughout the system, whereas in the other conditions direct surgery is usually preferred to prevent local increases in pressure which may cause brainstem dysfunction.

The cardinal feature of the Dandy-Walker syndrome is deficient development of the cerebellum (Fig. 26). In the complete syndrome the vermis and hemispheres are affected, whereas in the so-called variant the vermis alone is involved. There is usually in addition, membranous obstruction to the outlet of the fourth ventricle, causing a cystic space in direct continuity with the ventricle. The membrane is commonly, but not invariably, complete, causing isolation of the ventricular system from the subarachnoid space.

The hypoplasia of the cerebellum is evident on CAT and its degree may be assessed. It may consist of two symmetrical or asymmetrical projections from the posterior part of the upper pons, representing the separated cerebellar hemispheres, or in the least marked variation there may simply be absence of the nodulus, which is recognized by an unusually wide gap between the lower parts of separated, but otherwise normal, cerebellar hemispheres. The Dandy-Walker syndrome may be associated with partial or complete agenesis of the corpus callosum. The large cyst of c.s.f. attenuation in continuity with the fourth ventricle often balloons the posterior fossa and displaces the tentorium superiorly, causing separation and lateral displacement of the occipital horns. Superficially similar changes may occur with large central posterior fossa arachnoid cysts. The distinguishing features are that the fourth ventricle is separated from the cyst and the cerebellum is either normally developed and displaced or deformed by the cyst or shows focal hypoplasia adjacent to it (Figs. 19 and 27). Arachnoid cysts in general are recognized as rounded or irregularly shaped regions of similar attenuation to that of c.s.f. which show no enhancement (Banna, 1976). Their extracerebral situation is easily recognized in all regions, except for those arising in the suprasellar and quadrigeminal cisterns. These may be confused with dilatation of the third ventricle and its recesses, but the width of the cysts is usually greater than that of the ventricle and this is a helpful feature in differentiation. The cysts in other situations are associated with focal hypoplasia or displacement of the adjacent brain (Fig. 28); they frequently expand the vault and, by virtue of their position, may cause hydrocephalus.

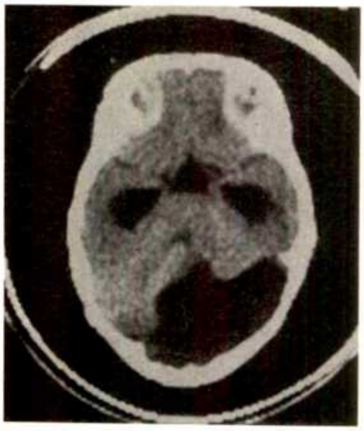

FIG. 27.

Arachnoid cyst over cerebellar convexity. Unenhanced scan. There is a large, fluid-filled cyst posterior to the right cerebellar hemisphere extending across the midline and expanding the overlying bone. The fourth ventricle is displaced anteriorly towards the left side by it. There is moderate dilatation of the ventricular system. The basal cisterns are normal.

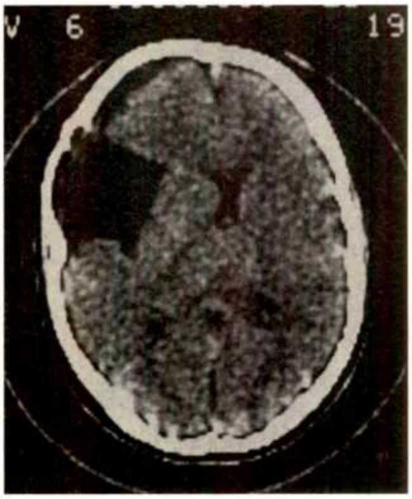

FIG. 28.

Left anterior temporal arachnoid cyst extending over inferior frontal convexity. The overlying vault is expanded and thinned. The left temporal lobe is hypoplastic and the cyst extends down to the insula, between it and the temporal and frontal opercula. The lateral ventricles are displaced slightly towards the right side.

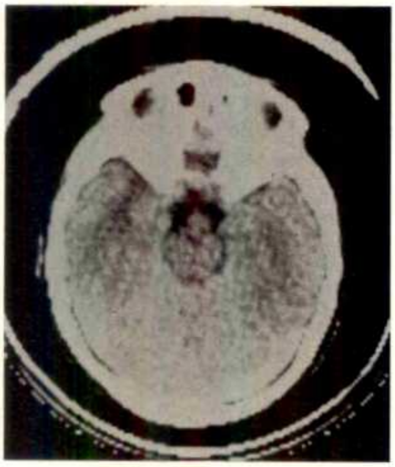

Fig. 29.

Hamartoma. Causes a small mass of brain attenuation within and above the interpeduncular fossa.

Tumours presenting within the first two months of life are classified as congenital (Arnstein *et al.*, 1951) and two gliomas in this category were examined but since they have similar features to the more common acquired ones they will not be discussed further. Other tumours arising at any time of life but derived from abnormal cell rests such as pineal teratomas and craniopharyngiomas are also too large a subject for inclusion. The low attenuation of lipomas is diagnostic, and precocious puberty associated with small masses of brain attenuation in the interpeduncular region is typical of hamartoma (Fig. 29).

Megalencephaly may be associated with spongiform degeneration and other hereditary leukodystrophies. It also occurs as an isolated feature with or without a family history of large heads. In these cases the excessive cerebral substance appears normal and the ventricles may be normal or slightly dilated. Up to the present time we have found no other abnormality in any cases with a benign family history of macrocrania, though we are continuing to evaluate them. In other groups CAT is necessary to exclude hydrocephalus and subdural haematoma.

About 50% of our paediatric CATs are normal; congenital malformations account for approximately 25% of the rest. Prior to CAT most of these cases were subjected to invasive procedures which are now rarely necessary for diagnostic purposes but may be indicated prior to surgery. The contribution of CAT to the management of these cases is apparent.

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Ioglycamide (Biligram) studies in man. Radiological opacification of the bile duct. A comparison of a number of different methods*

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ABSTRACT

Intravenous cholangiography was carried out in 80 anicteric patients using ioglycamide (Biligram). Twenty patients were given a 30 ml ampoule of 35% ioglycamide as a slow hand injection over ten minutes; the remainder were given ioglycamide by one hour slow drip infusion at a rate of 2, 3 or 4 mg per kg body weight per minute. The radiological opacification of the bile duct was then assessed independently by two radiologists. There was a statistically significant difference between the bile duct opacification found in patients given either 3 or 4 mg/kg/min of ioglycamide for one hour compared with those given ioglycamide either by ten minute injection or by 2 mg/kg/min drip infusion.

Drip infusion techniques have largely supplanted bolus injection methods for intravenous cholangiography. This is partly because drip infusion is associated with fewer side effects (Feldman and Keohane, 1966; McNulty, 1968; Ansell and Faux, 1973), and partly because there is some evidence that drip infusion gives better visualization of the bile ducts (Bornhurst *et al.*, 1968; Payne, 1968; Allen, 1969). Some workers have, however, failed to show any difference in bile duct opacification between the two methods (Darnborough and Geffen, 1966; Margolin and Obata, 1968; Scholz *et al.*, 1975).

In a recent survey (Bell *et al.*, 1975) we found that infusion rates for cholangiography varied from as much as 15 mg/kg/min to as little as 2 mg/kg/min. In an attempt to establish an optimal rate of infusion we have recently studied the biliary concentration of iodine following various rates of infusion of ioglycamide to patients with a T-tube *in situ* (Bell *et al.*, 1978). This study has shown that an optimum concentration of iodine in the common bile duct can be obtained when ioglycamide is infused at a rate of 4 mg/kg/min for one hour. The biliary iodine concentration achieved at this infusion rate was about 25% higher than that found when ioglycamide was infused at 2 mg/kg/min. A similar difference has been shown between the iodine concentration in the bile following infusion at a rate of 4 mg/kg/min and that following a ten minute injection of 30 ml of 35% ioglycamide (Biligram). These findings in man have confirmed our previous results in the rhesus monkey (Whitney and Bell, 1972, 1976).

The present study was designed to show whether the 25% greater biliary iodine concentration achieved at the higher infusion rate was accompanied by an observable improvement in bile duct opacification. We have taken a series of anicteric patients referred for intravenous cholangiography and assessed the opacification of bile duct achieved as a result of performing the investigation, (a) by a bolus injection or (b) by drip infusion using a range of different infusion rates.

MATERIALS AND METHODS

The patients

Only patients with a serum bilirubin below 25 mmol/l (1.5 mg/100 ml) and a serum alkaline phosphatase below 300 i.u./l (normal laboratory range 25–100 i.u./l) were included in the study. The age and weight of each patient was recorded, as was the kilovoltage used for radiography. In those patients given ioglycamide by drip infusion the rate of intravenous administration of the contrast agent was controlled using an IVAC 531 pump (Ivac Corporation, Harrow, Middlesex).

The following four groups of patients were studied.

(1) *Ten minutes bolus injection of 30 ml 35% ioglycamide—20 patients.*
Films were taken 20, 30, 40 and 60 minutes after the end of the injection.

(2) *One hour drip infusion of ioglycamide at a rate of 2 mg/kg/min—20 patients.*

(3) *One hour drip infusion of ioglycamide at a rate of 3 mg/kg/min—20 patients.*

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*This work had received the approval of the St. Bartholomew's Hospital Ethical Committee and the informed consent of the patients was obtained before the investigations were performed.

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Research carried out whilst holder of the Mackenzie Mackinnon Streatfield Research Fellowship.

(4) *One hour drip infusion of ioglycamide at a rate of 4 mg/kg/min—20 patients.*

In all three infusion groups the first film was taken within ten minutes of the end of the infusion while further films were taken as indicated over the next 60 minutes.

Radiological assessment

The two radiologists (I.K.F. and J.F.) graded the films without knowledge of the technique used to perform the cholangiogram. The best film from each patient's cholangiogram was taken and the opacification of the bile duct assessed. The opacification of the duct was assessed by each of the two radiologists independently and scored on a scale from 0 (no visualization) to 4 (excellent visualization). The intermediate grades 1, 2 and 3 represented opacification judged to be poor, moderate or good respectively. The mean of the scores for each of the two radiologists was recorded as a final score for each patient.

Statistical comparison of the radiological assessments

For statistical comparison the films were divided into three groups. Those with a mean score of 0, 0.5 or 1.0 were grouped together and graded as failed/poor. Those with a mean score of 1.5, 2.0 or 2.5 were grouped together and graded as moderate opacification, while the films with a mean score of 3.0, 3.5 or 4.0 were classified as showing good visualization of the bile duct. The total number and percentage of patients having cholangiograms which were graded as either (a) failed/poor (b) moderate or (c) good were then calculated for each group studied. The statistical comparison of these differences was then assessed using the X-squared test.

RESULTS

Ten minute bolus injection of 30 ml 35% ioglycamide (10.5 g)

In this group there were five males and 15 females. The mean age was 50.1 years (range 25–87) and the mean weight was 65.9±13.5 kg. The mean kV used was 74.4±1.7. The mean serum bilirubin and alkaline phosphatase levels were 9.1±5.0 mmol/l and 91.3±55.0 i.u./l. respectively.

One hour infusion of ioglycamide at 2 mg/kg/min.

In this group there were 11 males and nine females. The mean age was 56.8 years (range 28–76) and the mean weight was 70.0±13.4 kg. The average patient received a total of approximately 8.4 g of ioglycamide. The mean kV used was 76.6±1.8. The mean serum bilirubin and alkaline phosphatase levels were 10.8±5.1 mmol/l and 73.6±23.7 i.u./l respectively.

One hour infusion of ioglycamide at 3 mg/kg/min.

In this group there were eight males and 12 females. The mean age was 47.3 years (range 21–71) and the mean weight was 69.5±9.9 kg. The average patient received a total of approximately 12.5 g of ioglycamide. The mean kV used was 75.6±1.4. The mean serum bilirubin and alkaline phosphatase levels were 9.0±6.0 mmol/l. and 93.0±67.0 i.u./l respectively.

One hour infusion of ioglycamide at 4 mg/kg/min.

In this group there were seven males and 13 females. The mean age was 55.3 years (range 25–79) and the mean weight was 63.9±11.0 kg. The average patient received a total of approximately 15.3 g of ioglycamide. The mean kV used was 75.9±2.2. The mean serum bilirubin and alkaline phospatase levels were 11.0±6.0 mmol/l and 101.0±85.0 i.u./l respectively.

Radiological assessment

On the 0–4 scale the two radiologists gave 40 of the examinations the same score. Radiologist A gave higher scores than Radiologist B in 16 cases, and Radiologist B gave higher scores than A in 24 cases. The difference between the two independent assessments was ±1 grade in 36 cases and ±2 grades in four cases.

TABLE I

RADIOLOGICAL ASSESSMENT OF BILE DUCT OPACIFICATION

	Mean radiological assessment of bile duct opacification			
	Failed or poor	Moderate	Good	No. of patients
Ioglycamide—bolus injection	5	5	10	20
Ioglycamide—1 h infusion 2 mg/kg/min	6	8	6	20
Ioglycamide—1 h infusion 3 mg/kg/min	0	13	7	20
Ioglycamide—1 h infusion 4 mg/kg/min	0	9	11	20

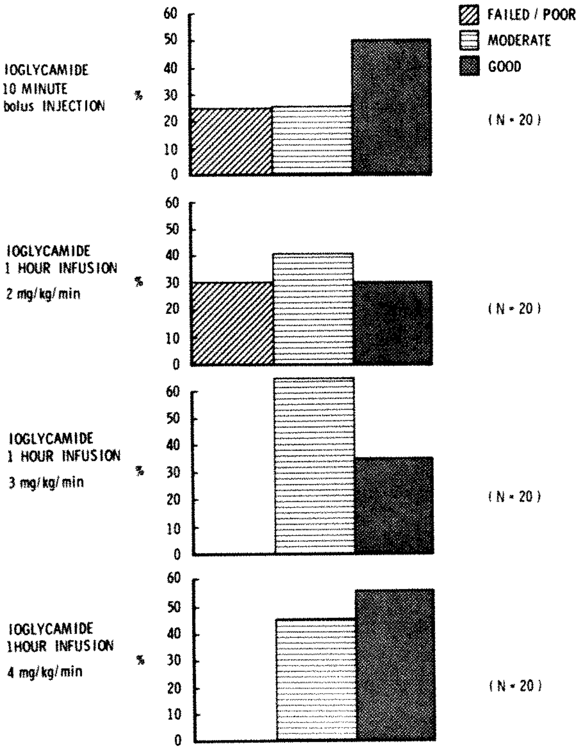

FIG. 1.

Radiological assessment of bile duct opacification—cholangiogram performed using ioglycamide. There is no difference between the ten minute bolus injection method and a one hour intravenous infusion at 2 mg/kg/min. When the infusion rate was increased to either 3 or 4 mg/kg/min then there were significantly less technically unsatisfactory examinations—see text.

TABLE II

STATISTICAL COMPARISON OF BILE DUCT OPACIFICATION

Groups to be compared	$\times^{2}_{2}{}^{x}$	p value
Ioglycamide bolus injection *v.* 1 h drip infusion 2 mg/kg/min	1.78	N.S.
Ioglycamide 1 h infusion 3 mg/kg/min *v.* 1 h infusion 2 mg/kg/min	7.27	0.03
Ioglycamide 1 h infusion 4 mg/kg/min *v.* 1 h infusion 2 mg/kg/min	7.53	0.03
Ioglycamide 1 h infusion 3 mg/kg/min *v.* bolus injection	6.01	0.05
Ioglycamide 1 h infusion 4 mg/kg/min *v.* bolus injection	6.19	0.05
Ioglycamide 1 h infusion 4 mg/kg/min *v.* 1 h infusion 3 mg/kg/min	0.91	N.S.

The number of cholangiograms recorded as failed/poor, moderate or good is shown in Table I. The percentage of patient's cholangiogram films in each of these groups is illustrated in Fig.1.

Statistical comparison (see Table II)

There was no difference in the mean scores of the ioglycamide ten minute bolus injection group when compared with the group of patients given ioglycamide as a one hour drip infusion at a rate of 2 mg/kg/min. The mean scores of the patients given ioglycamide at a rate of 3 mg/kg/min for one hour was significantly better than those given only 2 mg/kg/min for a similar length of time. Similarly, the mean score of the 20 patients given 4 mg/kg/min for one hour was significantly better than the 20 patients given only 2 mg/kg/min. The mean scores of the patients in the 3 mg/kg/min and 4 mg/kg/min were both significantly better than those of the 20 patients given a ten minute bolus injection of ioglycamide. It can be seen from Fig.1 that the main differences between the 3 and 4 mg/kg/min groups and either the 2 mg/kg/min infusion group or the ten minute bolus injection method is the 25 to 30% reduction in the number of technically unsatisfactory examinations. (*i.e.* the failed/poor group with a mean score of 1.0 or less). There was no difference in the mean bile duct opacification of the 20 patients given 4 mg/kg/min when compared with the 20 patients receiving only 3 mg/kg/min.

It is general experience that the opacification of the bile duct achieved in the heavier, more obese patients tends to be inferior to that achieved in the lighter, thinner subject. Because the mean body weights of each group are not quite comparable we correlated the patient's weight in each group of 20 patients with the mean score for the cholangiogram and Spearman's Rank correlation coefficient was computed. None of the four groups of 20 ioglycamide patients had values which were significantly different from zero.

Side effects

Of the 20 patients given a ten minute injection of ioglycamide (10.5 g), three patients experienced nausea and felt faint during the injection, one patient developed an urticarial skin eruption and two patients complained of a metallic taste in the mouth. No patient in any of the three ioglycamide infusion groups complained of feeling faint or experienced nausea during the infusion of the contrast agent. A slight metallic taste in the mouth was noted near the end of the one hour infusion by four patients—two patients had received ioglycamide at the rate of 3 mg/kg/min while a further two patients were given 4 mg/kg/min.

Discussion

The results of this study show that it is possible to reduce the number of technically unsatisfactory intravenous cholangiograms significantly by infusing ioglycamide at a rate of 3 to 4 mg/kg/min for one hour. We have previously shown that in patients with a T-tube *in situ*, near maximum biliary concentrations of the compound were obtained by infusing the ioglycamide intravenously at a rate of 4 mg/kg/min for 60 minutes (Bell *et al.*, 1978). When an infusion rate of only 2 mg/kg/min was used the resulting concentration of ioglycamide (and hence iodine) in the bile were about 75% of that achieved using the 4 mg/kg/min régime (Bell *et al.*, 1978). It is clear from the present results that relatively small changes in the concentration of contrast material in the bile duct can be detected radiologically and might be clinically important.

The visualization of the bile duct in those patients given a ten minute injection of 10.5 g ioglycamide was very similar to that achieved when ioglycamide was given via a drip at a rate of 2 mg/kg/min for one hour. When the rate of the one hour drip infusion was increased from 2 to 3 mg/kg/min, however, the resulting radiographs were significantly better than those obtained by the hand injection technique. The difference between the results obtained by the two cholangiographic methods was even more marked when the one hour infusion was performed at a rate of 4 mg/kg/min.

The rate of intravenous administration of the cholangiographic agent is clearly of importance, since too slow a drip rate will fail to give optimal biliary concentrations of iodine while too rapid a rate of infusion is likely to be associated with an increased incidence of toxic side effects. Differences in the actual rate of infusion and the total time taken to administer the contrast agent may explain some of the conflict in the literature regarding the relative efficacy and safety of the drip infusion and hand injection methods for performing intravenous cholangiography (Darnborough and Geffen, 1966; Feldman and Keohane, 1966; Wax and Crummy, 1966; Wangermez and Wangermez, 1967; Bornhurst *et al.*, 1968; Cooperman *et al.*, 1968; Foy, 1968; Margolin and Obata, 1968; McNulty, 1968; Russell, 1968; Nolan and Gibson, 1970; Moss *et al.*, 1973; Scholz *et al.*, 1975).

Scholz *et al.* (1975) studied four dosage régimes for performing cholangiography using iodipamide. The highest infusion rate used by them was (for an average 70 kg patient) of the order of 10 mg/kg/min over a 30-minute period. This infusion rate was 2½ times the maximum rate used in the present study and not surprisingly therefore, their patients suffered from a much higher incidence of side effects.

The results of our present study in anicteric patients do not permit us to make any recommendations regarding the optimal rate for administering ioglycamide to jaundiced patients. Whether the slow overnight drip infusion cholangiography method recently advocated by Fuchs and Preisig (1975) can be further improved by other infusion régimes awaits further study.

On the basis of our findings both in this study and also those previously reported in patients with a *t*-tube *in situ* (Bell *et al.*, 1978) we recommend that in anicteric patients an intravenous cholangiogram using iogylcamide is best performed using a one hour drip infusion method rather than a ten minute bolus injection technique. The ioglycamide should be administered at a rate of 3 to 4 mg/kg/min. In an average 70 kg patient, infusion rates of this order can be achieved by giving the patient a 100 ml bottle of the commercially available 17% Biligram over one hour.

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Book review

Recommendations of the International Commission on Radiological Protection. Annals of the ICRP. Vol.I, No.3. ICRP Publication 26, 1977 (Oxford, Pergamon Press), pp. v + 53, $10.00.

This publication embodies the latest basic recommendations of the ICRP, and replaces ICRP Publication 9 published 11 years ago. The new document is nearly twice the length of its predecessor, reflecting perhaps the increasing complexity of the issues involved in radiological protection. Not only are new units introduced (the sievert as the unit of dose-equivalent, 1 Sv = 100 rem), but also new terminology. Radiation effects are classified as stochastic and non-stochastic. The former include such effects as the induction of malignancies and hereditary damage where the risk may increase progressively with increasing dose and there is no threshold. Non-stochastic effects are those whose severity may increase with dose, but only above a quite high threshold dose. Cataract of the lens, non-malignant damage to skin and impairment of fertility fall in this category.

Much more emphasis is now placed on the importance of justifying every procedure involving radiation exposure, and to do this the benefits to be expected must be weighed against the detriment that may be caused. The protection for any procedure must also be "optimized" to ensure that radiation exposures are not only kept below the specified dose limits, but are kept "as low as reasonably achievable, economic and social factors being taken into account". The current vogue of cost-benefit analysis is therefore advocated with some suitable algebraic expressions thrown in to give an illusion of precision to a reality which is still bound to be very imprecise and subject to personal value judgements.

The term dose-equivalent limit (DEL) is now to be used instead of maximum permissible dose. For the radiation worker the annual DEL for uniform whole-body exposure remains the same, namely 50 mSv (5 rem), but the previous quarterly limit of 3 rem and the formula limiting the dose equivalent at age N years to $5(N-18)$ rem have now been removed from the recommendations. Most of the limits for tissues and organs irradiated singly have been raised (from 50 to 200 mSv for gonads is an example). An exception is the DEL for extremeties, which are no longer listed separately and must therefore be controlled by the value of 500 mSv for skin.

Unfortunately the reader has to dig quite deeply to elucidate such basic facts. There is no helpful summary table of dose limits as appeared in ICRP Publication 9, and the text as a whole is far less readable. It is doubtful if many radiologists (to whom the section on medical exposure is particularly relevant) or even hospital physicists will ever take the trouble to read the document right through. A similar conclusion may have been reached by the National Radiological Protection Board which has thoughtfully produced a very useful summary (NRPB—R63, HMSO, 1977).

J. L. HAYBITTLE.

1978, *British Journal of Radiology*, *51*, 196–202

Thecal deformity after lumbar myelography with iophendylate (Myodil) and meglumine iothalamate (Conray 280)

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ABSTRACT

A study of repeat myelograms carried out in 93 patients revealed that the incidence of thecal scarring following Conray lumbar radiculography is high (61% of all cases), and only slightly lower than that found after Myodil myelography (74%). Possible factors affecting the incidence of arachnoiditis and the radiological and clinical significance of this condition are considered.

Thecal deformity is the radiological manifestation of chronic arachnoiditis which has long been recognized as a complication of myelography with the oil-based contrast medium, iophendylate (Myodil) (Hurteau *et al.*, 1954; Davies, 1956). This iatrogenic condition has been implicated as the cause of chronic signs and symptoms referable to the lumbar spine (Halaburt and Lester, 1973; Suolanen, 1975). Consequently, many radiologists attempt to aspirate Myodil immediately after using it (Ritchie and Sinclair, 1972; Peterson, 1975). The favourable reception in the 1960s, and subsequent acceptance of the water-soluble contrast agents meglumine iothalamate (Conray 280) and its dimer, meglumine iocarmate (Dimer X), for lumbosacral radiculography were based as much on the belief that they were safer (Gonsette and André-Balisaux, 1968; Ahlgren, 1969; Praestholm and Lester, 1970), as upon their undoubtedly greater yield of diagnostic information (Occleshaw and Holyland, 1971; Grainger *et al.*, 1971).

Subsequent reports from Scandinavia indicated that the risks of thecal scarring with the meglumine salts is also significant (Autio *et al.*, 1972; Halaburt and Lester, 1973; Irstam, *et al.*, 1974). These reports coincide with the introduction of metrizamide (Amipaque, Nyegaard), a substance which Skalpe and Amundsen (1975) claim is non-toxic to the spinal cord and meninges. A multicentre analysis of repeat water-soluble myelograms of 138 patients who had previously undergone metrizamide myelograms, reported by Grainger *et al.* (1976), revealed only one instance of thecal scarring, which was found in a patient submitted to interval surgery.

An attempt is made in this paper to assess the long-term effects of Myodil and Conray myelography upon the spinal theca, by comparing the appearances of the initial and repeat myelograms of patients who were first examined with one of these substances, and attempting to determine the incidence of thecal scarring attributable to the contrast medium.

CONTRAST ARACHNOIDITIS AND CRITERIA FOR ITS DIAGNOSIS

The radiological appearance of the lumbar theca damaged by water-soluble contrast media has been recognized in recent years and several authors claim that it forms a distinct entity (Ahlgren, 1973; Irstam and Rosencrantz, 1973). Local deformities limited to the site of disc herniation and/or operation, such as root shortening, irregularity or blunting of root sheaths, may be the result of pre-existing pathology or operative trauma, thus they cannot be considered to be caused by the contrast medium. Identical changes may be seen after Myodil myelography but they may be difficult to identify if the repeat examination is also an oil myelogram or if an extensive operative procedure has been performed (Moseley, 1977).

The most subtle evidence of thecal fibrosis is shortening, smoothing and rounding of the root sheaths, which assume a blunted appearance, and in which the nerve roots themselves are not well seen (Fig. 1). These changes are bilateral and invariably first involve the sacral cul-de-sac and nerve root sheaths. Later the deformity is evident more cranially, affecting the lower lumbar root sheaths. It rarely extends above the level of the fourth lumbar vertebra and an abrupt transition from abnormal to normal theca can always be observed.

If the initial myelogram was made with Myodil, immobile oil residues in the form of droplets or streaks within the spinal canal or root sheaths may be seen. If the repeat examination is also an oil myelogram, these immobile residues may be the only evidence of a minimal arachnoiditis: the normal root sheaths do not fill well with Myodil and their apparent absence may not be significant.

A more advanced form, in terms of radiological severity, shows obliteration of root sheaths, a smooth silhouette and a sacral cul-de-sac that presents a

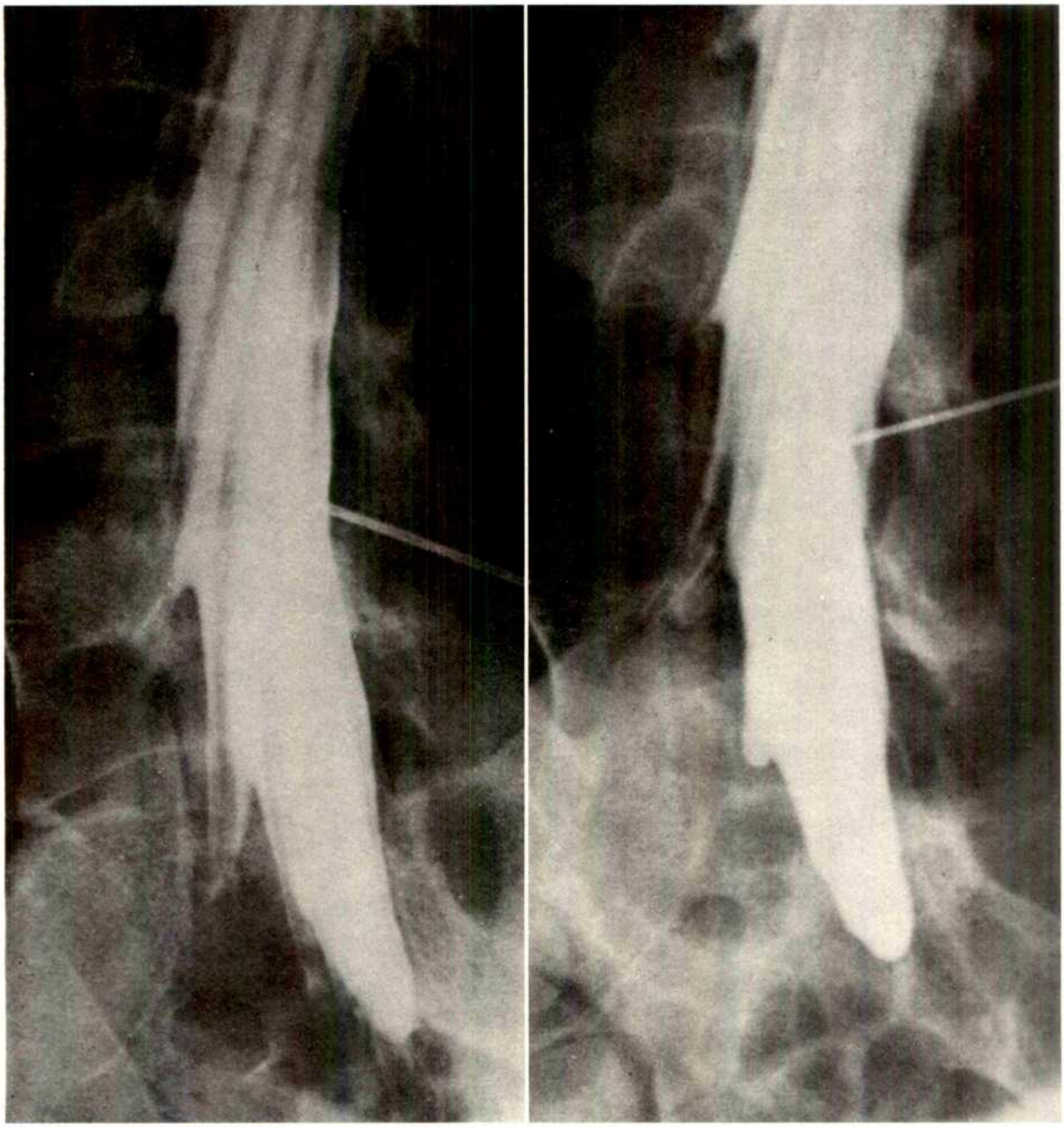
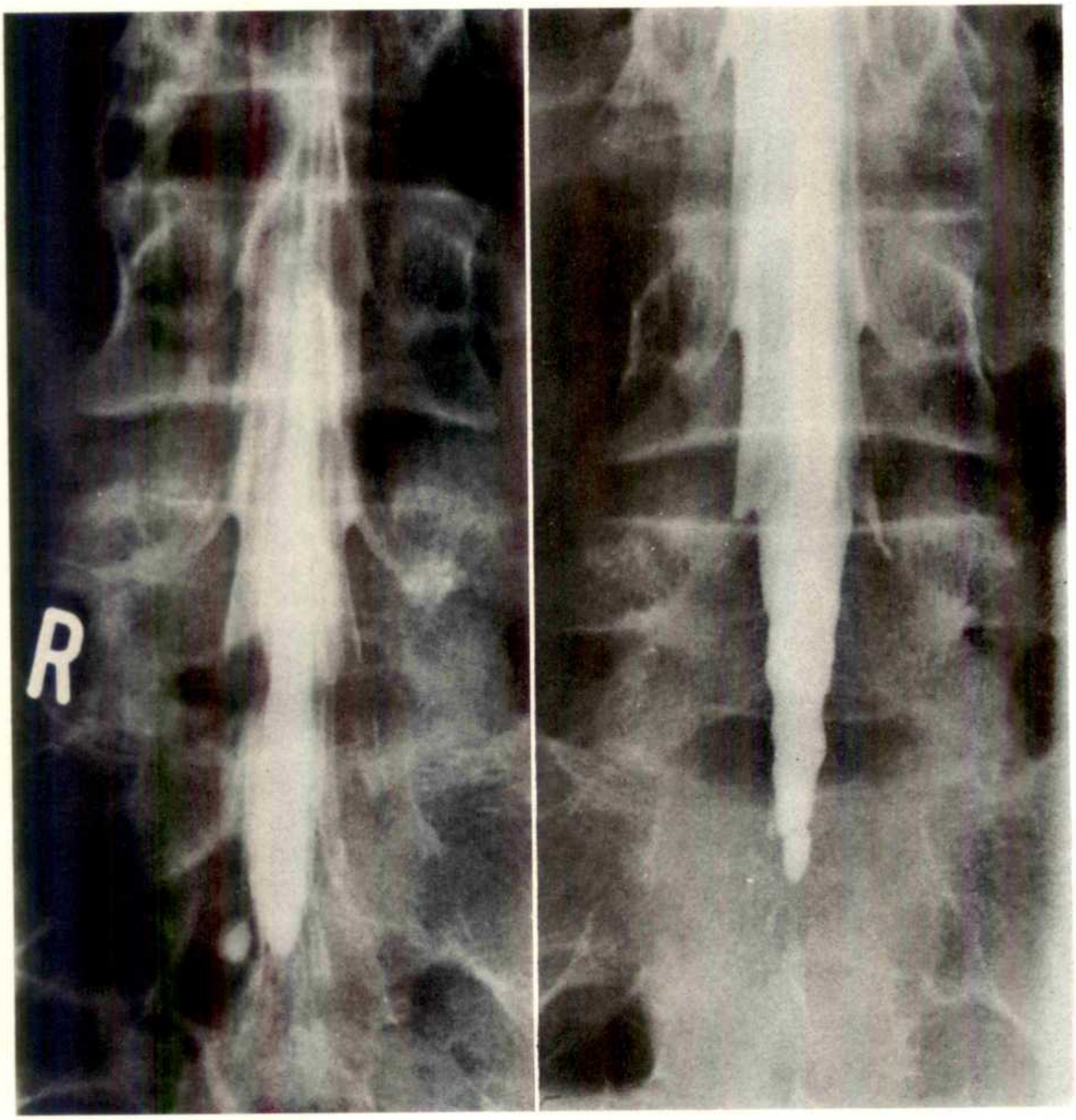


FIG. 1.

Conray arachnoiditis. (A) Initial examination with Conray 280. Oblique view showing normal appearances of root sleeves and nerves. (B) Repeat examination 28 months later, no interval operation. Same oblique projection shows obliteration of the caudal sacral root sleeves and blunting of the S1 nerve root pouch. Note dense homogeneity of contrast medium due to disappearance of the sacral fila radicularia. Fairly abrupt transition to normal appearances above this level.

homogenous appearance, the individual fila radicularia no longer being visible within the affected thecal space. The thecal tube may be narrowed concentrically and the cul-de-sac shortened; it may have a tapering "rat's tail" appearance and the outline is sometimes markedly irregular (Figs. 2 and 3). In the most florid form of scarring, there is complete obliteration of the thecal space and lumbar puncture fails.

All these features were noted in the patients in this series. In a number, abnormally thickened nerve roots were observed within the contrast



A FIG. 2. B

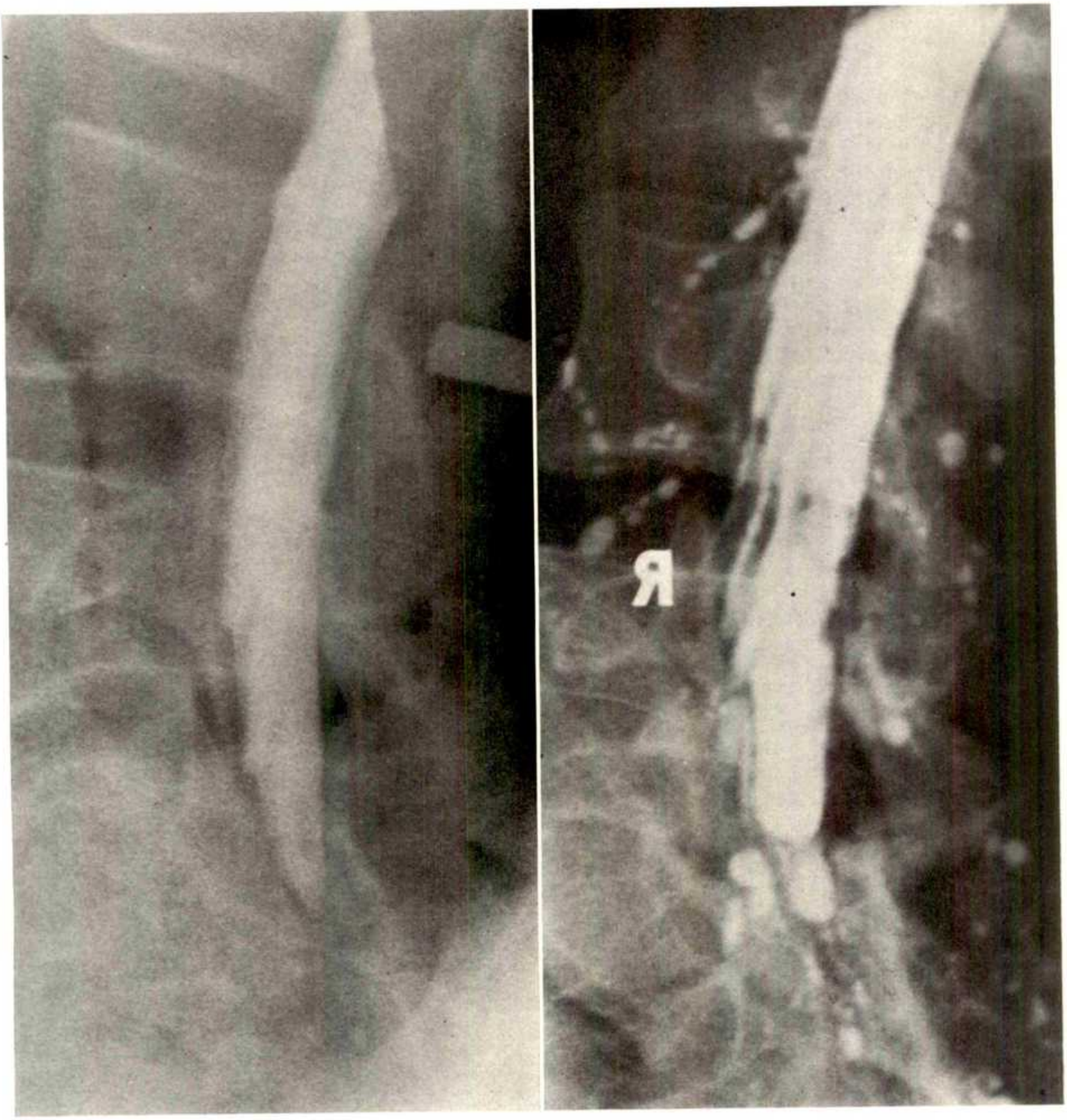
Dimer arachnoiditis. (A) Initial examination with Dimer-X. Frontal view showing lumbosacral disc protrusion, compressing the right nerve root. The sacral root sleeves and a small cyst outline well. (B) Repeat examination 13 months later, no interval operation. Note gross constriction of the lower thecal tube and shortening of the sacral cul-de-sac, producing an irregular "rat's tail" silhouette.

column above the level of the transition from damaged to normal theca. The criteria used to reach the diagnosis of contrast arachnoiditis are: (1) blunting of root sheaths; (2) absence of root sheaths; (3) homogeneity of sacral cul-de-sac (absence of the fila radicularia); (4) constriction of the thecal tube; (5) adherent oil residues.

PRESENT SERIES—METHODS AND RESULTS

During the past five years 1620 myelograms have been performed in the Wessex Neurological Centre, Southampton, of which 600 were water soluble lumbar radiculograms. Conray 280 was used for all but a few of the latter and Myodil for all the oil examinations. A proportion of these patients was examined more than once, and a total of 93 was collected in whom the radiographs of the first and second examinations were available for comparison. Excluded from the series were patients who had been submitted to myelography, operation or spinal injection prior to the initial examination.

In nearly all the initial myelograms, 8 ml of Myodil were injected and the entire spine was



A FIG. 3. B

Myodil arachnoiditis. (A) Initial examination with Myodil. Oblique view showing normal appearances. The root sleeves fill poorly but the fila radicularia are well seen within the thecal tube. (B) Repeat examination with oil six months later, no interval operation. Note three features of adhesive arachnoiditis: fixed oil droplets within the sacral canal and along the root sheaths; marked irregularity of the thecal tube which is constricted and loculated caudally; and matting of the nerve roots, shown here at the L4-5 level. Above this deformity, the thecal tube and its contents outline normally.

examined with the patient in the prone, supine and erect positions. In only two of these patients was the contrast medium aspirated at the end of the procedure. Nearly all the water-soluble radiculograms were performed with the patient erect: the rest were carried out in the semi-erect position (45 deg to the horizontal). An adequate volume of contrast medium was injected to opacify the thecal sac to the level of the L2-3 disc space. In about one-quarter of the examinations the contrast medium was mixed with 2 ml of cerebrospinal fluid prior to injection. After the examination as much as possible of the opacified fluid was drawn off, but this usually amounted to only a few ml lying above the level of the needle.

The time interval between first and second myelograms was noted, as well as interval events such as laminectomy, disc excision or epidural injection. Manipulations under anaesthetic and traction were classified as part of conservative management. Cerebrospinal fluid analysis was performed in each patient. Traumatic punctures were noted as being technically difficult: in one instance uniformly blood-stained cerebrospinal fluid was still obtained at the end of the procedure.

During interpretation attention was paid to the criteria for the radiological recognition of contrast arachnoiditis but in each case the diagnosis of thecal scarring depended on the authors being able to demonstrate incontrovertible changes between the first and second myelograms which could be attributed to the initial contrast medium. The results are set out in Tables I and II.

DISCUSSION

Several factors may influence the incidence of thecal scarring following myelography.

(1) *Choice of contrast medium*

A tabulated review of the results of other series (Table III) confirms the present author's findings in respect of the incidence of thecal scarring after Conray radiculography. Since Ahlgren (1973) in his patients found that Dimer X caused even more scarring than Conray—55% compared with 47%—it would appear that there is little to choose between the two commonly used water-soluble media; both are equally hazardous in this respect, and only slightly less likely to scar the theca than Myodil.

The average volume of contrast medium required in the erect patient to opacify the theca to the level of the L2-3 disc space is 9 ml and doses of this magnitude are used regularly in the Wessex Neurological Centre. Slätis *et al.* (1974) have shown that the osmolarity of the cerebrospinal fluid increases with increased volumes of contrast medium, and that this rise in osmolarity is most marked and more persistent caudally. By showing that thecal scarring is greatest where there has been the largest rise in fluid osmolarity during myelography, and that this rise is greater with larger contrast volumes, it may be inferred that the incidence of thecal scarring is directly proportional to the volume of contrast medium used. Support for this view comes from the results of Irstam *et al.* (1974), who found a low incidence of thecal scarring in patients in whom only 4 ml were injected. Similarly, Ahlgren (1973) reported a positive correlation with volume for Dimer X when used in volumes larger than 6 ml. However, he was unable to demonstrate a convincing correlation between scarring and volumes of Conray up to 7.5 ml. Despite Ahlgren's negative results, the authors believe that contrast volume is probably a significant factor in the production of thecal scarring, certainly in large doses.

TABLE I

Incidence of thecal deformity following Myodil myelography

	Total numbers of patients	Numbers (and percentage) showing thecal scarring
Myelography only. No operation or procedure	18	12 (66%)
Myelography and laminectomy	34	27 (80%)
Myelography and epidural injection	2	1 (50%)
Total	54	40 (74%)

TABLE II

Incidence of thecal deformity following Conray radiculography

	Total numbers of patients	Numbers (and percentage) showing thecal scarring
Radiculography only. No operation or procedure	20	10 (50%)
Radiculography and laminectomy	16	11 (68%)
Radiculography and epidural injection	3	3 (100%)
Total	39	24 (61%)

TABLE III

INCIDENCE OF CONTRAST ARACHNOIDITIS FOLLOWING CONRAY RADICULOGRAPHY: COMPARISON OF RESULTS

	Patient totals (operated and non-operated) excluding epidurals	Numbers showing positive signs (operated and non-operated)	Incidence of arachnoiditis as percentage (operated and non-operated)
Halaburt and Lester (1973)	46 (33 + 13)	12 (—)	26.1% (—)
Ahlgren (1973)	76 (58 + 18)	36 (28 + 8)	47.4% (48% + 44%)
Irstam, Sundström, Sigstedt (1974)	25 (13 + 12)	4 (3 + 1)	16.0% (23% + 8%)
Southampton (1977) series	36 (16 + 20)	21 (11 + 10)	58.3% (68% + 50%)

(2) *Technical aspects*

Traditionally, the presence of blood in the cerebrospinal fluid was regarded as a contra-indication to myelography because of the increased risk of arachnoiditis (Howland and Curry, 1963). More recent work challenges the view that blood raised the incidence of chronic arachnoiditis following oil or water-soluble examination (Ritchie and Sinclair, 1972; Jacobson, 1973). In the present series, no correlation was found between traumatic lumbar puncture and subsequent thecal scarring.

Aspiration of Myodil is widely practised and advocated (Peterson, 1975) but the removal must be complete, if the procedure is to be of any value. This manoeuvre was never universally adopted in England, and in the present series there are only two patients in whom a wholly successful aspiration of Myodil was achieved, and both subsequently showed thecal scarring! The miscible properties of the water-soluble media make total removal impossible, and the sacral cul-de-sac invariably remains densely opacified. Of five patients in whom a large volume of opacified cerebrospinal fluid was removed (about 5 ml, compared with 9 ml of Conray injected), four showed subsequent scarring.

(3) *Interval laminectomy and epidural injection*

Lumbar laminectomy may give rise to a diffuse arachnoiditis, irrespective of whether the theca is pierced at operation and irrespective of the amount of extradural bleeding (Smolik and Nash, 1951; Epstein, 1968). In the present series, both in the Myodil and in the Conray group, an interval procedure significantly increased the incidence of thecal deformity (80% compared with 66% for Myodil; 68% compared with 50% for Conray). This finding confirms those of Ahlgren (1973) and Irstam *et al.* (1974). The high incidence of scarring found in operated cases may therefore merely represent an aggregate total from two different causes.

Five patients underwent interval epidural injection and four showed thecal scarring upon repeat examination. Arachnoiditis has been reported after spinal anaesthesia in a few cases (Kennedy *et al.*, 1945; Greene, 1961).

(4) *Time elapsed between myelographic examinations*

The average interval between examination in the Conray group was 16 months in those patients with positive signs of thecal scarring. By comparison, conservatively managed patients examined initially with Myodil with positive evidence of scarring were re-examined after an average interval of only seven months. This finding may indicate that thecal scarring develops more rapidly following the use of Myodil than after Conray. It is possible that if the Conray patients had been examined later still, more cases of thecal scarring would have been found.

(5) *Clinical significance of thecal scarring*

What is the significance of the thecal scarring found upon repeat myelography in the patient with chronic back pain? Previous authors, notably Jørgensen *et al.* (1975) have found no good correlation between the symptomatology, radiological appearances and surgical findings in patients in whom a radiological diagnosis of chronic arachnoiditis is made. In a few cases it has been implicated as the cause of the symptoms (Halaburt and Lester, 1973; Suolanen, 1975). Although no definite symptom complex of contrast arachnoiditis can be defined, it may undoubtedly confuse the clinical picture and complicate management, either by producing symptoms due to nerve root tethering and fibrosis or by disguising a co-existing prolapsed intervertebral disc.

Hirsch, *et al.* (1969) in discussing the importance of changes limited to the root sheaths, found that nearly two-thirds of the changes in their series were caused by disc herniation. Clearly therefore, disc protrusions may be hidden by root sheath obliteration due to thecal scarring from a previous myelogram. It is important to recognize the diagnostic limitations of myelographic examination of the scarred theca. Secondly, the diagnosis of contrast arachnoiditis should not be attached to a segment of obliterated root sleeves, if the root sleeves caudal to it show a normal appearance.

Other causes of thecal scarring, apart from contrast arachnoiditis, may be encountered in patients undergoing repeat myelography *e.g.* infection and infestation; and carcinomatous and lymphomatous infiltration may mimic it.

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Book review

Dermatologic Radiotherapy. By O. Braun-Falco, H. Goldschmidt and S. Lukacs, pp. xiv+154, illus., 1976 (Springer Verlag), DM.35·40.

This is an excellent publication covering in a concise, easily readable way the principles of radiotherapy in skin diseases. In particular, an up-to-date account of the place of radiation therapy in benign dermatoses and pre-malignant conditions is welcome. As might be expected, a book of this standard also deals very adequately with the radiotherapy of cutaneous tumours. All sections are well illustrated with diagrams and there are many colour prints.

The physical basis of radiation therapy is well covered and often explained with the aid of simple diagrams. Those relating percentage depth dose for various radiations to the anatomical structure of the skin and subcutaneous tissues are particularly informative. Dose factors and tissue tolerances are explained, and recommended schedules for various conditions are given. There is a good index and full bibliography. This small volume should fill an important place in the libraries of dermatological as well as radiotherapy departments.

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1978, *British Journal of Radiology*, *51*, 203–205

Pneumatosis coli in non-Hodgkins lymphoma

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ABSTRACT

Two patients with poorly differentiated lymphoma who developed pneumatosis coli are described. In one case, the intramural gas was associated with diffuse nodular submucosal deposits of tumour. An annular stricture due to lymphoma was the underlying aetiology of the pneumatosis coli in the second case. The pathogenesis of pneumatosis coli in the context of malignant lymphoma is discussed.

Pneumatosis cystoides intestinalis is an uncommon condition characterized by the presence of gas in the submucosa or subserosa of the bowel. Any portion of the gastro-intestinal tract may be involved, but when the aberrant collections of gas are confined to the colon, the term pneumatosis coli is applied. There are many known causes of pneumatosis cystoides intestinalis, and these have been well-described in a recent review of the subject (Olmstead and Madewell, 1976). In the context of diffuse malignant lymphoma, the diagnosis of pneumatosis coli may have important implications; it may indicate (1) ischaemic necrosis, possibly secondary to severe anaemia or hyperviscosity syndrome, or (2) an acute necrotizing colitis due to an infectious agent (Olmstead and Madewell, 1976). In childhood leukaemia, typhlitis, a form of pneumatosis intestinalis, has been described (Borns and Johnston, 1973; Wagner *et al.*, 1970) and is thought to be due to denuded Peyer's patches, secondary to steroid therapy.

In widespread lymphoma, a further aetiology of pneumatosis coli is suggested. We have recently seen two patients with diffuse malignant lymphoma with colonic involvement, who developed pneumatosis coli. The association has not been previously noted.

CASE REPORTS

Case 1

A 57-year-old, white male presented with general malaise and widespread lymphadenopathy. On examination, in addition to the enlarged cervical, axillary, and inguinal lymph nodes, he was found to have hepatosplenomegaly and an epigastric mass. A peripheral blood film and a bone marrow aspirate revealed many poorly differentiated lymphocytes. A subsequent lymph node biopsy established a diagnosis of poorly differentiated lymphocytic lymphoma. Other investigations, including a gallium scan, abdominal ultrasound, intravenous urography, and a chest radiograph, indicated that the pathological staging was IVB. A barium enema was performed because of rectal bleeding. This revealed diffuse nodularity throughout the colon due to tumour deposition and extensive pneumatosis coli predominantly in the ascending and traverse colon (Fig. 1). A subsequent rectal biopsy confirmed the submucosal lymphoma infiltration. The patient was started on quadruple chemotherapy, and a barium enema repeated eight months after the initial examination showed no abnormality.

Case 2

A 58-year-old, white male was seen in The University of Chicago Hospitals and Clinics two years after a diagnosis of poorly differentiated lymphocytic lymphoma had been made

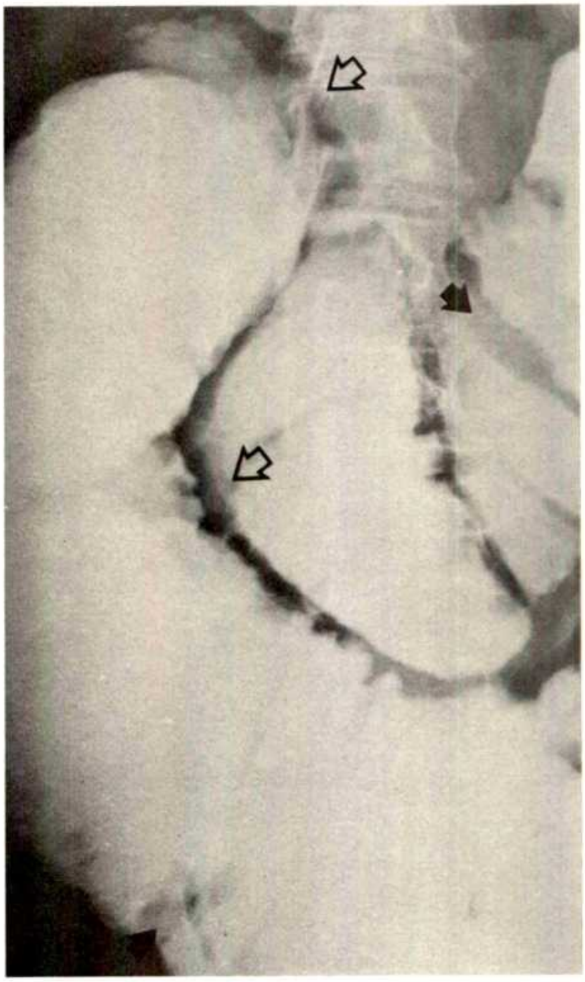

FIG. 1.

There are nodular masses of tumour in the ascending and transverse colon (closed arrows). The intramural gas is arrowed (open arrows).

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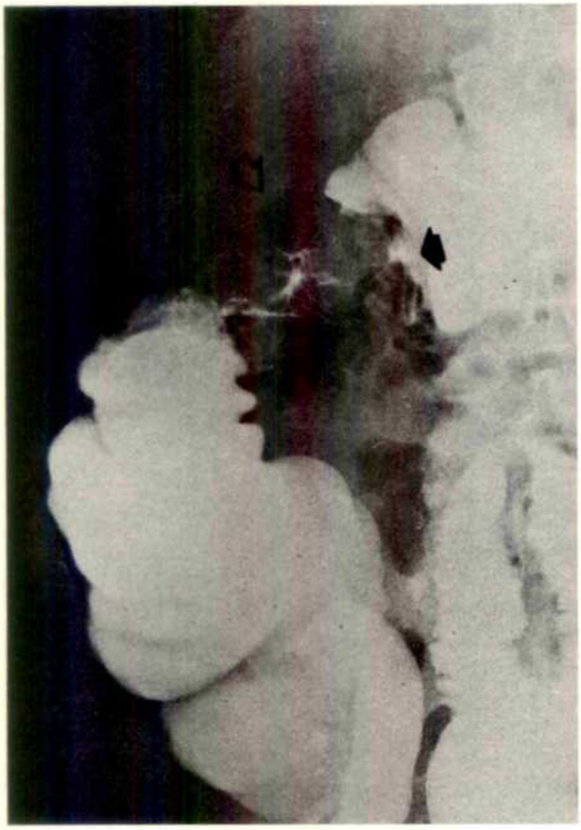

FIG. 2A.

There is an annular stricture in the proximal transverse colon (closed arrows) with adjacent pneumatosis coli. Note also the gas cysts in the ascending colon (open arrows).

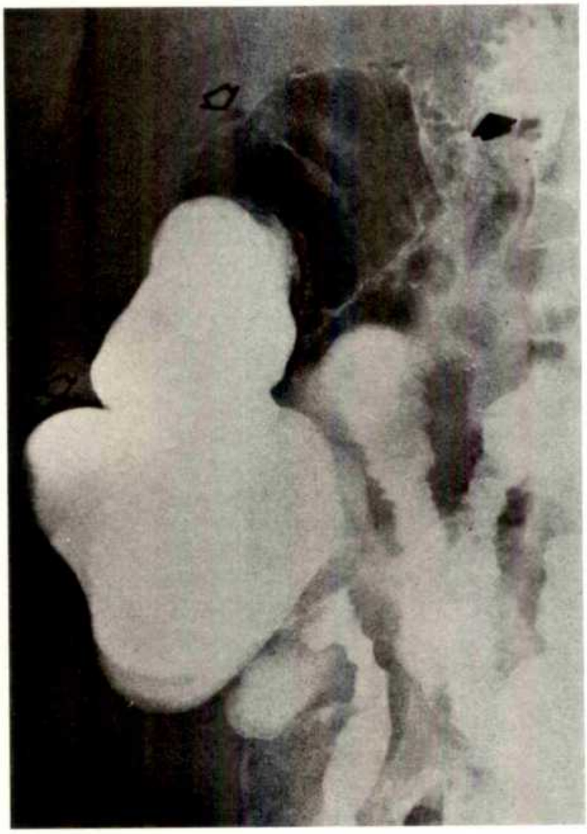

FIG. 2B.

The proximal portion of the stricture can be clearly seen with the associated pneumatosis coli.

elsewhere. He had been treated with local radiotherapy. Fever, night sweats, and weight loss were the presenting symptoms, and subsequent investigations revealed pulmonary involvement with lymphoma and hepatosplenomegaly. He was treated with chemotherapy, but 12 days after starting treatment he developed abdominal pain and diarrhoea. A plain abdominal radiograph demonstrated pneumatosis coli in the caecum and ascending colon, but there was no evidence of intestinal obstruction. The chest radiograph revealed persistence of the pulmonary lymphoma but no pneumothorax or pneumomediastinum. The patient's condition remained unchanged, and a barium enema was performed 12 days after the initial diagnosis of pneumatosis coli. The pneumatosis coli was confirmed, and there was, in addition, an annular stricture in the transverse colon, which was not apparently causing significant intestinal obstruction (Figs. 2A, B, and C). At necropsy three days later, the caecum and ascending colon contained multiple gas cysts, and the colonic stricture was proven histologically to be due to lymphoma.

DISCUSSION

Previous reports have enumerated many causes of pneumatosis coli (Olmstead and Madewell, 1976). In cases where no underlying cause is found, an association between pneumatosis coli and chronic airways obstruction has been documented (Forgacs *et al.*, 1973). Airways obstruction, however, was not a factor in our two cases. When local pathology is associated with pneumatosis coli, the colonic lesion is generally of an obstructive, ulcerative, or ischaemic nature.

Diffuse lymphoma infiltration, as seen in our first case, suggests a further underlying aetiology. The pathogenesis of the pneumatosis coli is perhaps analogous to the association of pneumatosis coli and collagen diseases, notably diffuse systemic sclerosis (Mueller *et al.*, 1972). The common denominator may be the disruption of the submucosal anatomy of the colon. Since colonic lymphoid tissue is situated between the submucosa and the lamina propria, it is possible that these deposits of lymphomatous tissue distort and devitalize portions of the mucosa, allowing air to track into the bowel wall.

Vague abdominal pain and diarrhoea led to a plain abdominal radiograph and a diagnosis of

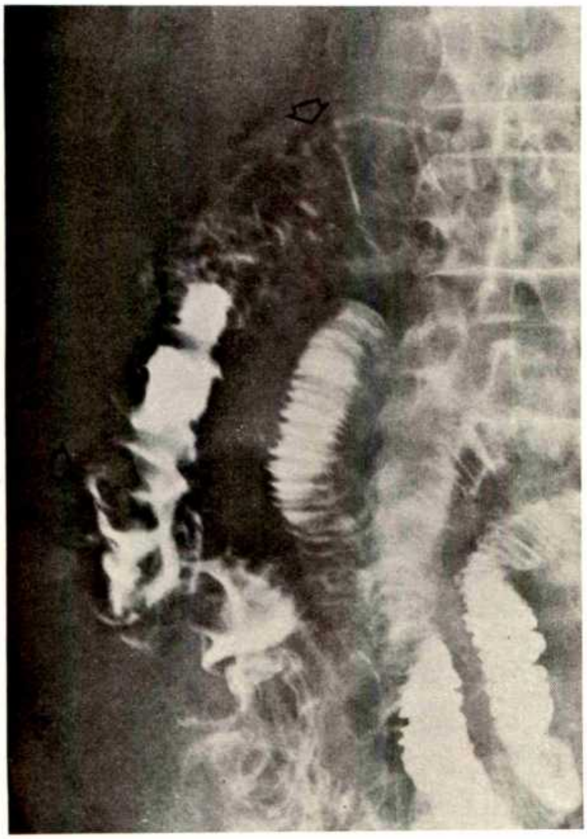

FIG. 2C.

Post-evacuation radiograph. Intramural gas cysts can be seen in the caecum and in the ascending and proximal portion of the transverse colon (open arrows).

pneumatosis coli in Case 2. As the clinical findings did not support the presumptive diagnosis of bowel infarction, a barium enema was performed. This revealed a malignant stricture in the transverse colon with pneumatosis coli proximally. Postmortem examination showed that the stricture was due to local deposition of submucosal and subserosal lymphoma.

Previously described intestinal obstructions, when associated with pneumatosis coli, have usually been evident clinically and radiologically because of their severity (Shallal *et al.*, 1974). Case 2 had neither clinical nor radiological features to suggest a significant obstruction. Two possibilities therefore may explain the pneumatosis coli in this case: (a) the direct effect of tumour infiltration as in Case 1, or (b) minor episodes of obstruction, not apparent radiologically.

In a patient with known malignant lymphoma, the radiological demonstration of pneumatosis coli, as seen in the cases described, may be of considerable importance. It may indicate the presence of hitherto unsuspected colonic involvement, which will significantly alter the patient's staging, treatment, and prognosis.

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Book review

Development of Angiography and Cardiovascular Catheterization. By T. Doby, pp. xiv + 205 and 25 figs, 1976 (Publishing Science Group Inc., Littleton Mass., U.S.A.), $18.00.

This is an unusual medical history book, but one which radiologists who practise angiography will find difficult to lay aside. The first chapter reviews the development of knowledge about the vascular system from Ancient Greece to the time of Roentgen. The later chapters describe the development of angiography and cardiovascular catheterization and the men responsible. Dr. Doby has researched his subject in depth, and has produced many fascinating details about the early workers in the field of angiography. Pride of place naturally goes to Egas Moniz who created two manual disciplines, cerebral angiography and psychosurgery, but because of his arthritic hands could perform neither himself! Similar interesting and human details are provided concerning men like Dos Santos, Forssmann and Castellanos. The book is strongly recommended to angiographers and to all interested in the history of medicine.

DAVID SUTTON.

1978, *British Journal of Radiology*, *51*, 206–209

Clinical trial of four pancreatic scanning agents

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ABSTRACT

Four ^{75}Se-labelled amino acids have been tested in 22 patients. In 11 of the patients pancreatic function was estimated by the Lundh test.

Scans at varying time intervals up to 30 hours from isotope administration were assessed by blind marking. Pancreatic visualization with all four agents was markedly poorer than would have been expected with ^{75}Se-selenomethionine. Whole-body retention was estimated for all four agents; two showed faster ^{75}Se clearance than selenomethionine. Radioactivity in duodenal aspirate was measured for two of the agents.

^{75}Se-labelled compounds produced by the Radiochemical Centre have been submitted to clinical trial at several hospitals. This paper reports the results obtained at one centre with four of the compounds (Table I).

PATIENTS STUDIED

Permission for the study was obtained from the Committee on Safety of Drugs in Medicine and from the hospital's Ethics Committee; fully informed consent was obtained from the patients. In seven patients scanning with a trial agent was performed simultaneously with a routine Lundh test and ^{75}Se levels in the duodenal aspirate were also measured. Fifteen patients were scanned without simultaneous duodenal intubation; four later had a routine Lundh test.

Eleven of the 22 patients studied were considered to have normal pancreatic function on follow-up for a period of one to two years. Two patients had chronic pancreatitis with a severely abnormal Lundh test and two had impaired pancreatic function with a moderately abnormal Lundh test. One patient was diabetic, one had haemochromatosis and one a carcinoma of the common bile duct; in the remaining four diagnosis was uncertain.

TABLE I
THE TRIAL AGENTS

Radiochemical Centre Code	Compound
SCD6	Se-(2-aminoethyl)-L-selenocysteine
SCD7	Se-methyl-L-selenocysteine
SCD9	L-selenoethionine
SCD11	"DL-selenotryptophan" 2-amino-3-(3-benzo(b) selenophenyl) propionic acid

METHODS

All patients were scanned within one hour of intravenous administration of 3 μCi per kg body weight of the trial agent. A five-inch crystal rectilinear scanner was used with a scanning speed of 26 cm/min; anterior and posterior views were recorded for each scan. Many patients also had repeat scans at varying time intervals up to approximately 30 hours (Table II). Twelve had liver scans with either ^{99}Tc^{m} sulphur colloid or ^{198}Au gold colloid.

Three experienced observers assessed all the trial scans by blind marking together with 40 ^{75}Se-selenomethionine scans as controls. Each observer independently recorded any possible uptake in pancreas, liver, kidney, spleen or small bowel together with an assessment of the scan as if it had been obtained with ^{75}Se-selenomethionine—*i.e.* whether the pancreas appeared normal or whether it showed a moderate or severe generalized reduction in uptake or a filling defect. All the results quoted are based on the majority verdict of the observers.

A limited amount of whole-body counting was performed on 12 patients using a simple single crystal counter with the patient sitting at 1 metre from the crystal face.

Measurements of ^{75}Se concentration in duodenal aspirate over a two-hour period in the seven patients who underwent a simultaneous Lundh test were compared with previously established control values for ^{75}Se-L-selenomethionine (Youngs *et al.*, 1971). Trypsin in duodenal aspirate was assayed by the method of Levin *et al.* (1972).

RESULTS

Scans (Table III)

Uptake in the liver was noted in all scans with SCD6 and SCD9 and in most of the scans with SCD7 and SCD11. Kidney uptake was most frequently reported with SCD11 but was also seen with SCD6.

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TABLE II

SCANS PERFORMED

Compound	No. of patients	No. scanned at 0–1 h	1–2 h	2–6 h	20–30 h	No. of patients who also had colloid liver scan	later ^{75}Se-selenomethionine scan	Lundh test
SCD6	9	9	1	3	1	6	4	3
SCD7	4	4	2	0	1	2	1	2
SCD9	6	6	3	3	2	4	1	5
SCD11	3	3	1	2	0	0	0	1

TABLE III

RESULTS OF BLIND SCAN REPORTING

	No. of patients	No. of scans	Possible uptake reported in Pancreas	Liver	Kidney	Spleen	Bowel	Interpretation as selenomethionine scan Normal	Poor uptake or filling defect	Little or no uptake
SCD6	9	14	1	14	4	0	3	0	2	12
SCD7	4	7	0	6	0	1	4	0	0	7
SCD9	6	14	0	14	0	1	4	0	0	14
SCD11	3	6	2	5	4	0	2	0	1	5
SM scans on patients in trial	6	6	4	6	0	0	4	2	2	2
Control scans with SM										
(i) normal patients	20	20	20	20	0	0	1	19	1	0
(ii) pancreatic disease	20	20	5	19	0	0	1	1	6	13

Nineteen patients—including all those scanned with SCD7 and SCD9—showed no evidence of any pancreatic uptake in any scan. Two of the three patients scanned with SCD11 appeared (on blind reporting) to show possible pancreatic uptake in their first scans. However both scans were reported abnormal by selenomethionine standards. Subsequent re-interpretation by the same observers with the information that high levels of ^{75}Se appeared rapidly in the urine with this compound strongly suggested that the poorly defined uptake initially interpreted as pancreatic was more probably in the right kidney. Similarly the only case of possible pancreatic uptake with SCD6 may have corresponded to kidney uptake; the scan was abnormal by selenomethionine standards.

The control selenomethionine scans showed one "false-positive" report in 20 normal patients and one "false-negative" report in 20 patients with proven pancreatic disease; pancreatic uptake was reported in all the normal patients but in only five of the patients with disease. Six of the patients scanned with a trial agent were later scanned with selenomethionine; only two (one with haemochromatosis and one of unknown diagnosis) failed to show pancreatic uptake.

Whole-body retention (Fig. 1)

A short term study suggested that whole-body ^{75}Se clearance with SCD7 and SCD9 was roughly comparable to that with selenomethionine.

In contrast only about 50% of administered radioactivity was retained at 24 hours with SCD6. Clearance with SCD11 was even faster with only about 5% retained at 24 hours. Urine collections (two patients) with this compound contained respectively 33% and 42% of the administered radioactivity within two hours.

Duodenal aspirate (Fig. 2)

Altogether 11 patients had Lundh tests. Three (two with chronic pancreatitis and one with carcinoma of the bile ducts) showed severely subnormal duodenal trypsin; five were consistent with some impairment of pancreatic function and three were normal.

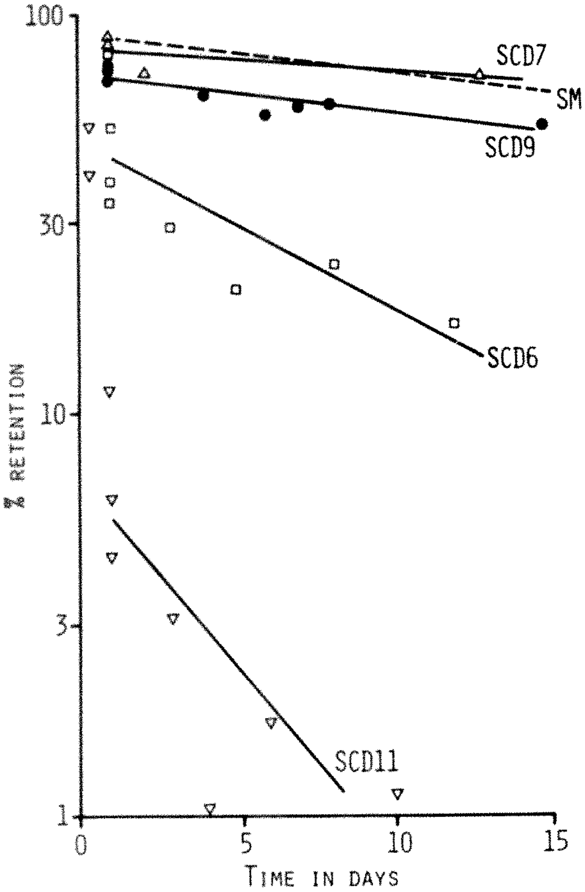

Fig. 1.

Whole-body retention (corrected for physical decay) of the four agents: □SCD6 (five patients), △SCD7 (two patients), ●SCD9 (four patients), ▽SCD11 (three patients). The dashed line (SM) indicates mean retention for selenomethionine (Lathrop *et al.*, 1972).

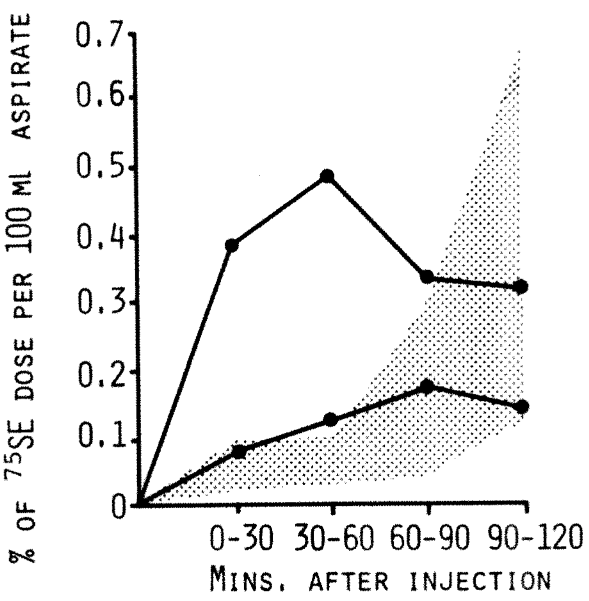

Fig. 2.

Concentration of ^{75}Se in duodenal aspirate for two patients with SCD6. The upper line is for a patient with normal duodenal trypsin, the lower for one with mildly subnormal trypsin. The shaded area indicates the normal range for selenomethionine (Youngs *et al.*, 1971).

Two patients scanned with SCD6 showed duodenal ^{75}Se levels comparable with the normal range for ^{75}Se-selenomethionine, although apparently reaching an earlier peak. Five patients given SCD9 showed markedly lower duodenal ^{75}Se levels—ranging from approximately 0.002 to 0.06% of dose per 100 ml of aspirate during the two hours following isotope administration—and no relationship could be detected between duodenal ^{75}Se and trypsin levels.

Discussion

^{75}Se-selenomethionine is a poor scanning agent. Many patients scanned with it fail to show any image of the pancreas because uptake depends on adequate exocrine function in the gland. A better agent might permit visualization in patients with impaired pancreatic function—although this would only be of practical use if at least the present level of discrimination between the normal and the abnormal pancreas was maintained. The selection of patients for this trial included a significant proportion with possible impairment of function. However, only three had severe pancreatic disease while 11 were classified as "normal" on follow-up. It thus seems reasonable to suppose that between 11 and 19 of the patients in the trial would have shown some pancreatic uptake had they been scanned with selenomethionine and, in fact, four out of six later scanned with selenomethionine did show an image of the pancreas. The almost complete failure of all four agents to provide any visualization of the pancreas in scans performed at varying time intervals after administration therefore virtually rules them out as possible replacements for selenomethionine.

Two of the agents in this trial, SCD6 and SCD7, were also studied by Tothill and Heading (1975) who visualized the pancreas in only one of three patients scanned with SCD7. With SCD6 and two other agents they tried—SCD8 (Se-ethyl-L-selenocysteine) and SCD10 (D-selenomethionine)—the pancreas was not seen.

The failure of the trial is particularly disappointing because initial animal experiments at The

Radiochemical Centre had suggested that each agent should have given at least as good pancreatic visualization as selenomethionine plus faster biological clearance and hence reduced radiation dose for the same administered activity; autoradiographic studies in mice with SCD11 had indicated a particularly high pancreas to liver uptake ratio (Marlow, 1974). However, published reports on ^{75}Se-selenomethionine uptake in four animal species (dog, monkey, rabbit and rat) show considerable inter-species variation in the ratio of pancreas to liver uptake, both in terms of concentration and of whole organ uptake (Zuidema *et al.*, 1963; Sodee, 1965; Awwad *et al.*, 1966; Melmed *et al.*, 1969); the ratio of pancreas to kidney uptake appears to vary even more. Similar inter-species variation must be expected with other ^{75}Se-labelled amino acids and probably accounts for the discrepancies between the preliminary animal experiments and the present clinical trial. The animal experiments were, of course, essential for checking the *potential* usefulness and toxicity of the SCD compounds.

As in a previous study on ^{75}Se-L-selenocystine and ^{75}Se-DLmeso-selenocystine (Melmed *et al.*, 1969), kidney uptake of the trial agents was a significant factor. When reduced whole body retention of a potential pancreatic agent merely reflects rapid elimination of isotope which has played no useful role in pancreatic imaging it must be seen as a disadvantage of the compound; the kidney image may partly overlap that of the pancreas. With ^{75}Se-selenomethionine, transport to the pancreas is linked to that organ's requirement of methionine for protein synthesis. Any further search for a new pancreas radiopharmaceutical must depend on studying in as much detail as possible the mechanisms of amino acid uptake in the pancreas (Tothill and Heading, 1975). In this trial SCD9 showed no pancreatic uptake *and* no possible release of labelled pancreatic enzymes into the duodenum. SCD6 did however in one patient show possible uptake in the pancreas and did show significant concentrations in duodenal juice. This *may* have corresponded to release of labelled pancreatic enzymes although it may equally have derived from the uptake seen in the liver.

Recent developments in other techniques for visualizing the pancreas—endoscopic retrograde pancreatography (ERP), CT scanning and ultrasound—have not eliminated the need for an effective radioisotope scanning technique. At present, scanning with selenomethionine can help in selecting patients for ERP in that a normal scan is an indication for not proceeding to the more hazardous test (Mitchell *et al.*, 1976). An improved scanning technique—whether resulting from methods of enhancing selenomethionine uptake (Lewander, 1976) or from a new radiopharmaceutical—could play a greater role in selecting patients for more hazardous or less readily available procedures.

Acknowledgments

We are grateful to all the patients in the trial for putting up with our rather time-consuming tests. We thank Dr. G. M. Cree and Mr. J. A. Peacegood of The Radiochemical Centre for their advice and help.

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Gonad dose in cineurethrocystography

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ABSTRACT

The technical factors used for cineurethrocystography for the true lateral projection in females are given. The mid-line radiation dose has been measured with LiF TLD inserted into the vagina in 19 examinations. The average dose recorded was 148 mrad, the range being 50 to 306 mrad; the average number of cine frames exposed was 96. Data obtained using a Rando phantom indicated that the average ovary dose would be 30% greater than the mid-line dose since the near ovary receives a higher dose than the more distant one.

The technique used for men is also given, the average gonad dose in six men being 123 mrad, range 56 to 243 mrad when simple lead foil gonad protection was used; the average number of cine frames was 107. The dose in one man without gonad protection was 1575 mrad for 112 cine frames. The results for both sexes compare favourably with those of others reported in the literature and with gonad doses recorded in typical IVP examinations.

Cineurethrocystography has been used in this Institute in the investigation of stress incontinence in women since 1954. Until 1973 the majority of patients, who were referred from gynaecological clinics, were menopausal or had previously had hysterectomies (Ardran *et al.*, 1956a, 1956b).

Initially, the X-ray studies used a 12.5 cm image intensifier and 35 mm cine camera with individual exposures at the rate of four per second for up to 100 frames (Ardran and Wyatt, 1957). The optical system consisted of two Taylor Hobson *f*/1.5 lenses used back to back with an effective aperture of *f*/0.7. Since about 1966 a 23 cm image intensifier has been used with the same camera and optical system. Originally (Ardran *et al.*, 1956a) it was estimated that the maximum gonad dose in the female would not be greater than 3 rad for 100 frames.

Since 1970, partly in collaboration with the Department of Urology (Ramsden *et al.*, 1976; Moolgaoker *et al.*, 1972), a series of investigations including cystometry and pressure/flow studies was combined with cinecystography. Many of the patients were in younger age groups and a number of males were included. For these reasons it was considered advisable to re-assess the level of gonad dose using lithium fluoride dosemeters placed in the vagina for women, or on the scrotum for men.

TECHNIQUE

In women the examination has always been carried out in the true lateral projection with the patient seated. For measurement of the vaginal dose three LiF chips were enclosed in a small plastic envelope placed in a finger cot which was attached to the end of a 15 cm length of polythene tubing; approximately 2 cm of lead wire of such diameter that it would not slip was introduced into the tubing and positioned so that it ended just proximal to the TLD. The stiff polythene tube allowed the enclosed chips to be inserted into the top of the patient's vagina while the free end could be attached to the nearside of the thigh with adhesive tape.

Men were investigated standing in the A.P. projection with one foot slightly raised, the leg externally rotated and the whole body slightly rotated in the same direction to obtain an oblique view of the urethra. The gonads were protected with 0.25 mm lead foil wrapped across the scrotum and fixed with adhesive tape; the TLD chips in their small plastic envelope were fixed with adhesive tape on the patient's side of the lead foil near the top so that it lay close to the root of the scrotum.

With a three-phase generator, typical exposure factors for females were 90 to 100 kV, 100 mA, individual frames being exposed for 0.05 to 0.06 sec. The males were examined using 65 kV, 100 mA, individual frames being exposed for 0.03 sec. The X-ray tube-focus to image-intensifier distance was 110 cm. Total X-ray tube filtration was 2.5 mm Al equivalent.

Harshaw LiF TLD – 100 chips, 3.2 × 3.2 × 1 mm thick, were used. Before use for dosimetry on patients the sensitivity of the chips was measured in air with 100 kV X rays over a range of exposures from 50 mrad to 2000 mrad, by comparison with the calibrated 35 ml ionization chamber of an EIL 37*c* dosemeter.

RESULTS

Women

Average vaginal dose in 19 examinations 148 mrad. Range 50–306 mrad. Average number of cine frames 96. These figures should be increased by 30% to give average ovary dose, see below.

TABLE I

DOSES TO OVARIES MEASURED IN A RANDO PHANTOM WITH 100 RAD ENTRANCE DOSE ON LEFT SIDE

Nominal kV	Penetrameter kV	L-ovary dose (rad)	R-ovary dose (rad)	Av. ovary dose (rad)	Mid-line dose (rad)	Ratio Av. ovary dose / Mid-line dose
100	87	11.3	2.0	6.65	5.0	1.33
90	80	8.26	1.37	4.81	3.86	1.25
80	70	7.35	1.13	4.24	3.20	1.33

Total filtration = 2.5 mm Al
FFD = 100 cm
FSD = 63 cm
Field area at surface = 23 × 18 cm

Men

Average dose in six men with gonad protection 123 mrad. Range 56–243 mrad. Average number of cine frames 107. Dose in one man without gonad protection 1575 mrad; cine frames 112.

Assessment of Results

In males we consider the method used to be sufficiently accurate for the purpose and the results show the considerable reduction in male gonad dose which can be achieved even by simple protection with thin lead foil.

In females the mid-line measured doses have to be corrected since one ovary is closer to the X-ray tube than the other. Wall (1976), using a Rando phantom, has made measurements of the ovary doses assuming the ovaries to be 5 cm from the mid-line and level with the upper border of the acetabulum. The conditions under which these measurements were made are given in Table I. Depth-dose absorption curves and data kindly supplied by Wall (1976) obtained for this quality of radiation indicate that the mid-line dose should be increased by approximately 30% to give the average gonad dose. We think that the measured mid-line dose, after correction, is a good indication of the maximum gonad dose the individual could have received. In practice, one gonad may frequently be shielded, at least for part of the examination, by contrast medium in the bladder, and on many occasions one or both ovaries may in fact be just outside the primary X-ray beam.

DISCUSSION

The gonad doses found in this survey are considerably lower than those originally estimated. This is largely because inadequate allowance was made previously for absorption by bone; the doses are low compared with those often reported by other workers because of our use of a 35 mm system giving 1–1 magnification on the film and because of the large aperture optical system employed. The results compare very favourably with gonad dose delivered in other procedures (Langmead *et al.*, 1976) in which the ovary doses for an IVP examination range from 67 mrad to 720 mrad while the male gonad doses range from 75 mrad to 1510 mrad.

Saenger *et al.* (1976) in their paper on cineurethrocystography in children state that in their series the ovary dose in girls was 85 to 1700 mrad, average 389 mrad, and in boys 9 to 158 mrad, average 44 mrad. Pratt *et al.* (1973) in the evaluation of 16 mm cinecystourethrography in children gave an ovary dose ranging from 153 to 697 mrad, average 366 mrad. In boys the gonad dose ranged from 26 to 158 mrad, average 77 mrad.

Kaude and Reed (1969) measured gonad doses in children in voiding cineurethrocystography using 70 mm image-intensifier fluorography, the ovary dose ranging from 352 to 1100 mrad, with an average of 566 mrad, and the gonad dose for boys ranging from 220 to 1531 mrad, average 785 mrad. One would expect the doses in children to be less than those in adults if the techniques were similar.

It would appear that the gonad doses with our technique are not excessive compared with other techniques or other diagnostic procedures.

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Book reviews

Cesium-137 from the environment to man: metabolism and dose. N.C.R.P. Report 52, pp. v + 48, 1977 (N.C.R.P., Washington), $3.00.

This latest addition to the N.C.R.P. report series deals with metabolism and dosimetry of ^{137}Cs which, because of its relatively long half-life and ready uptake into the body through food chains, is prominent in all considerations of the consequences of radioactive fall-out.

The report comprises four main chapters which concern: (a) the relationships between ^{137}Cs in the environment and in man, (b) the dosimetry of internally incorporated ^{137}Cs in man, (c) the derivation of the dose limits and maximum permissible concentrations in air and water for occupational exposure and (d) effects observed in two experiments on dogs injected with ^{137}Cs. The report concludes with a short summary.

Chapters (a) and (b) provide a reasonably referenced review of radiological protection from ^{137}Cs and its dosimetry in man. Beyond this I have reservations regarding the value of the report. Chapter (c) on dose limits will need to be reviewed in the light of the new I.C.R.P. recommendations (I.C.R.P. 26) also published this year. The experiments on dogs described in Chapter (d) concern very high doses delivered by single injections of ^{137}Cs and are therefore not very relevant to the most common problems encountered in radiological protection, *i.e.* the continuous exposure to relatively small doses resulting from contamination of the environment and of work places. Any value of these results for assessing the long term risks of large scale releases of ^{137}Cs is diminished by the absence of a table giving data on the late effects in controls.

It is doubtful whether the report will find application in the U.K. Levels of ^{137}Cs from fall-out have declined markedly over the last ten years. A forthcoming I.C.R.P. publication, announced in I.C.R.P. 26, will provide limits for intake of radioactive materials at work. Considerations for controlling the release of radioactive materials to the environment and assessing the effects of accidental releases will need to be reviewed in the light of I.C.R.P. 26 and the data in the Medical Research Council document "Criteria for controlling radiation doses to the public after accidental escape of radioactive material".

K. F. Baverstock.

Cancer and radiotherapy. A short guide for nurses and medical students. By J. Walter, pp. 271, 2nd edn., 1977 (Churchill Livingstone) £3·95.

This edition continues to do all that the sub-title indicates. In two respects the book does more. First, it is of use not only to nurses and medical students but also to graduates, for example physicians and surgeons wishing to know about current methods of treating malignancies. Second, more than radiotherapy is described, for there is useful detail on other methods such as cytotoxic and hormone therapy. Thus the book amounts to an introduction to modern oncology.

The first edition (1971) was the best text available in its class. The present edition is still the best which the reviewer has seen.

In this edition there have been additions in every chapter, particularly on the subject of cancers in childhood. A new chapter deals with advances in the management of leukaemias, Hodgkin's disease and other lympho-reticular disorders. Further, prostatic cancer, retinoblastoma and the acute radiation syndrome have new sections.

The plan of the book resembles that of the first edition; it begins with chapters on cancer, followed by those on the physics, biological effects and principles of radiotherapy. Malignant disease of specific sites or systems then receive several chapters. Amongst the later chapters are those on radioisotopes, on terminal care and on the management of pain. An envoi, though cautious, expresses in general a hopeful outlook for the future. The work ends with a brief list of derivations and a guide to further reading.

There are many illustrations, mostly line drawings or diagrams. They succeed in conveying their meaning clearly.

This book is a paperback and was printed in Singapore. The first edition was printed in Great Britain with a lighter type-face and with neat underlining of particularly important words or phrases. In the present edition italics replace the underlining. In this reviewer's opinion the italics do not attract the eye so effectively as did the underlining.

This useful guide should be available in every medical and nursing school. Other libraries and individuals interested in treating cancers will also wish to own this inexpensive, nicely balanced and yet comprehensive small volume.

Thelma D. Bates.

1978, *British Journal of Radiology*, *51*, 213–217 MARCH 1978

An improved technique for interstitial radiotherapy of the tongue*

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(*Received June, 1977*)

ABSTRACT

An improvement of the plastic tube afterloading technique for interstitial radiotherapy of the tongue is described. This modification allows most of the work to be done outside the patient's mouth. The anchorage for the intra-oral ends of the polythene tubes is produced by transfixing them with a silk thread. This obviates the need to form loops and simplifies afterloading. It provides a method for crossing the entire lingual end of the implant. All areas and volumes of lower jaw structures are accessible to this form of treatment. Removal of the implant, irrespective of position, is simple and rapid.

Interstitial radiotherapy of the tongue is beset by the difficulties of accurately placing and securing the radioactive sources. It commonly results in an uncomfortable implant with unsatisfactory dose distribution, and which is difficult to remove.

Intra-oral templates (Bier *et al.*, 1973; Sharett *et al.*, 1974; Nickel and Leake, 1975) for guiding the insertion and securing the position of radium needles, and a rigid radium needle device (Ellingwood *et al.*, 1976), have been described to improve the geometry, reduce the technical skill required, control the mobility of the tongue and reduce the swelling associated with interstitial implants. Due to the length and rigidity of the radium needles required, these methods are suitable only for treating anteriorly placed, relatively superficial tumours.

Pierquin (1964) and Paine (1972) have described the use of flexible radio-active wires with directional gutter guides for superficial tumours, and afterloaded implanted plastic tubes, using the loop technique, for larger penetrating tumours of the tongue.

Our modification of transfixing the intra-oral ends of the polythene tubes with a silk thread and crossing wire provides an intra-oral anchor and facilitates easy removal (Fig. 1). It eliminates the need to form a loop which is technically difficult to accomplish posteriorly in the mouth. It allows the entire implant to be crossed superiorly and provides a simple method of afterloading the vertical tubes without having to negotiate sharp bends in the loop. This method is technically simple and most of the work is done outside the patient's mouth.

MATERIALS

The following materials are used. (1) Radio-active iridium wire (diameter 0.3 mm) or tantalum wire (diameter 0.4 mm) cut to appropriate lengths. (2) Nylon inner tubing (I.D. 0.75 mm, O.D. 0.94 mm): (Flex Nylon size 1-Portex Limited, Hythe, Kent). (3) Gas-sterilised polythene outer tubing (I.D. 1.2 mm, O.D. 1.7 mm): (Intramedic Type PE 190—Clay Adams, Division of Becton, Dickinson and Co, Parsippany, NJ 07054, U.S.A.). (4) A number of trocars 12 to 15 cm long, with cannulae bevelled at one end, capable of accommodating the outer polythene tubing. (5) A Perspex plate introducer guide (template) to ensure parallel implantation of the trocars. This is a Perspex bar 1.25 cm thick into which a row of holes has been drilled perpendicular to the surface. The holes allow fairly tight passage of the trocars and are spaced 1 cm apart. Parallel planes can be implanted at the desired distance by inserting Perspex spacers between adjacent bars. (6) Nylon balls and lead discs for immobilizing the polythene tubes (Radiochemical Centre Code N202). (7) A number of 18 gauge hypodermic needles. (8) Silk thread (00) on a straight round-body sewing needle.

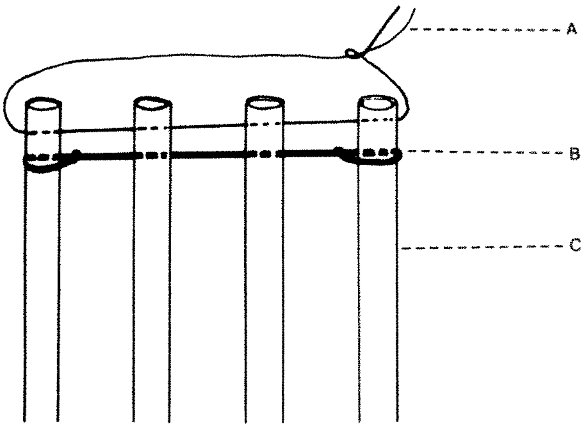

FIG. 1.

Schematic diagram of the intraoral end of the implant. A = silk thread; B = crossing wire; C = polythene tube.

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*Presented at the South African Society of Radiotherapists Congress, March 27, 1977.

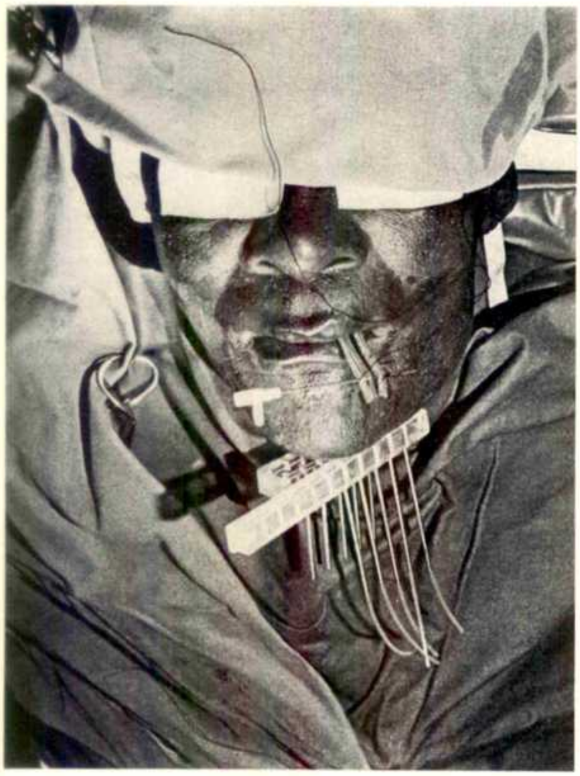

Fig. 2.

Photograph showing preparation of one plane of the implant. Note trocars traversing plastic template. Polythene tubes passed through trocars emerge from mouth where silk thread and hypodermic needle have transfixed tubes ready for afterloading the crossing wire.

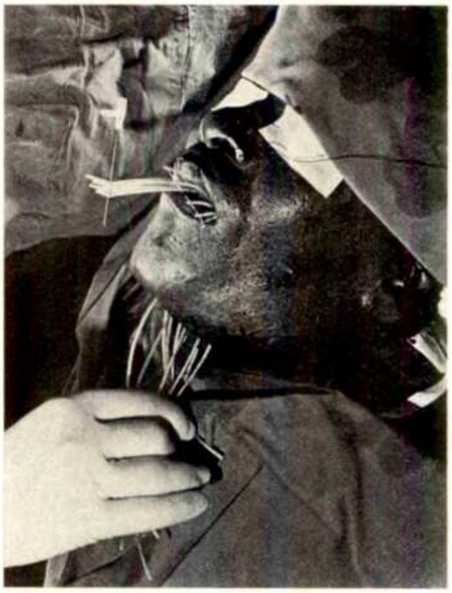

Fig. 3.

Photograph showing first plane with crossing wire being pulled back into mouth.

METHOD

The procedure is performed under general anaesthesia. The Perspex template is held against the skin in the submandibular region overlying the tumour area. Trocars with cannulae are pushed through the tumour volume using the template as a guide to ensure even and parallel implantation.

Either by direct vision, palpation or mirror examination, the trocars are checked to ensure that the desired area has been transfixed and the geometry is satisfactory. After removing the cannulae, the outer polythene tubes are introduced through the trocars and brought out through the mouth.

Outside the mouth, the tubes of one plane are transfixed with silk thread, from anterior to posterior, about 1 cm from their superior end. The free ends of the thread are tied together in a loop. If a crossing wire is required it is now introduced through the polythene tubes as close below the silk thread as possible. This is done by piercing the tubes with a hypodermic needle in this position (Fig. 2). The crossing wire is fed into the needle which is then withdrawn leaving the wire in place.

Before introduction, the crossing wire is cut 10 mm longer than the width of the implant so that, by bending back approximately 5 mm of each end around the outermost tubes, it is secured in position. The tubes are trimmed 1 mm above the silk. The trocars are withdrawn and the whole row of tubes is pulled down (Fig. 3), back into the mouth, until the crossing wire rests on the dorsum of the tongue. Additional planes are completed in the same way.

When the plane is wider than 6 cm, or is posteriorly placed, we have found it advantageous to divide the crossing wire into two portions. This makes manoeuvrability easier. The silk thread should still transfix the whole plane.

The distance from the crossing wire to the skin may be determined visually by pushing a suitably graduated guide wire into the polythene tubes. The appropriate length of radio-active wire to treat the tumour adequately over its whole depth, and to allow for subsequent tissue swelling, is cut and heat-sealed in the nylon inner tubes while the anaesthetic is being reversed.

The heat seal should not exceed 2 mm so that when cut and positioned the end of the vertical wire can be as close to the crossing wire as possible. Generally by the time the patient is awake, the inner tubes have been prepared and afterloading of the

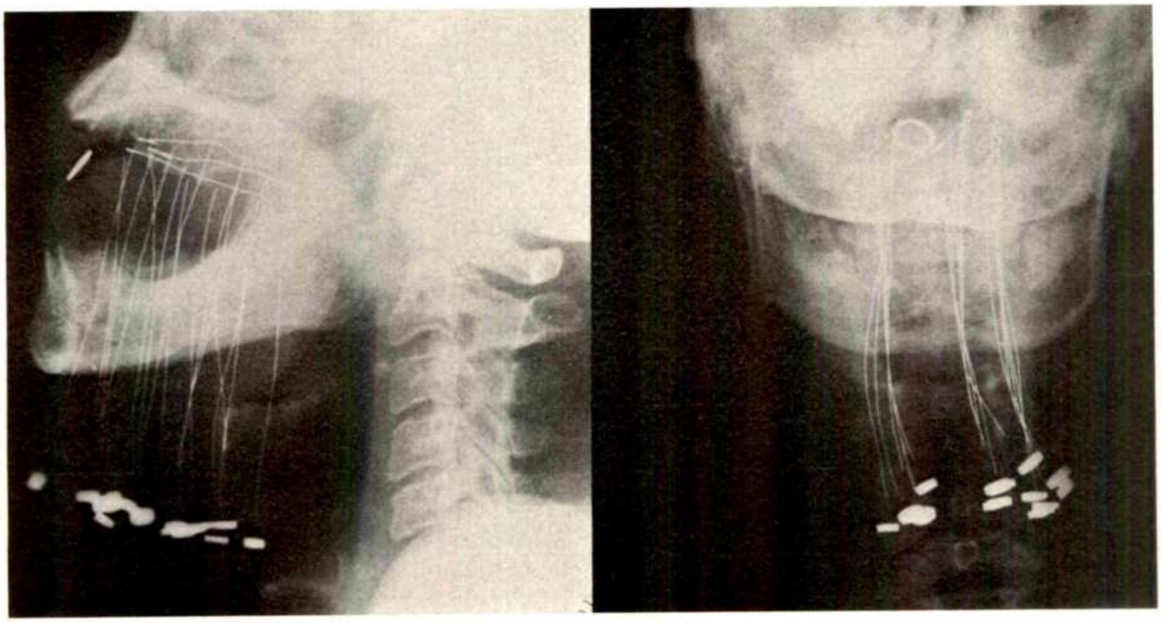

FIG. 4.
Radiograph of a three plane implant *in-situ*.

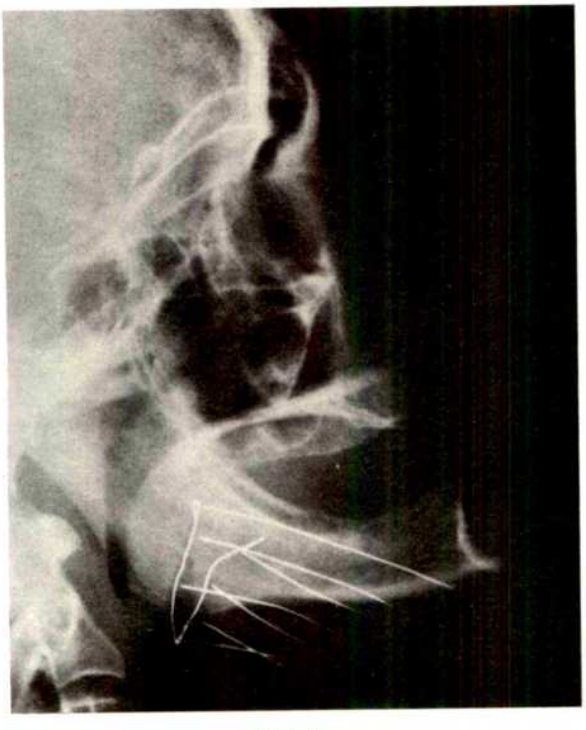

FIG. 5.
Radiograph of a two plane implant in the base of tongue.

implanted tubes can commence in an adjoining room.

Nylon balls to prevent pressure necrosis, together with lead discs, are applied to the outer tubes. A 1 cm gap between skin and ball is allowed to accommodate swelling of the injured tissues. The loaded inner tubes are fed into the outer tubes until they abut against the crossing wire. The position of the implant is checked radiographically (Figs. 4 and 5). The lead discs are crimped to prevent movement of the inner tubing in the outer and to secure the implant in position.

The removal of the implant is done by cutting the tubing between the balls and the lead discs. The balls are removed and the outer tubes cleaned with antiseptic solution. The silk thread lying on the dorsum of the tongue is firmly grasped with forceps and gently pulled upwards, allowing a whole plane to be withdrawn through the mouth in a single step. Only premedication with analgesics is required.

DISCUSSION

The problems associated with available interstitial techniques are summarized in Table I. Our method features the advantages of afterloading techniques, viz: reduced technical difficulties, absence of sutures,

TABLE I

PROBLEMS ASSOCIATED WITH DIFFERENT METHODS OF INTERSTITIAL RADIOTHERAPY IN THE TONGUE

		Temporary				
		Rigid		Flexible sources		
	Permanent	Radium needles				
	Seeds	Freehand	Intra-oral template	Gutter guides	Looped plastic tubes	Modification
Placement difficulty Anterior position Posterior position	 No Yes	 No Yes	 No Yes	 No Yes	 No Yes	 No No
Unreliable geometry	Yes	Yes	No	No	No	No
Inhomogeneity of dose to the dorsum of tongue	No	No	No	Yes	Yes	No
Implant stability Affected by tissue swelling and interference by anaesthetist	No	Yes	No	Yes	No	No
Need to suture	No	Yes	Yes	Yes	No	No
Afterloading difficulty	—	—	No	No	Yes	No
High radiation exposure to hands	No	Yes	No	Yes	No	No
Poor tongue mobility Difficult oral feeding and poor oral hygiene	No	Yes	Yes	No	No	No
Lack of radiographic control before implantation	Yes	Yes	No	No	No	No
Difficult to remove	—	Yes	No	No	No	No

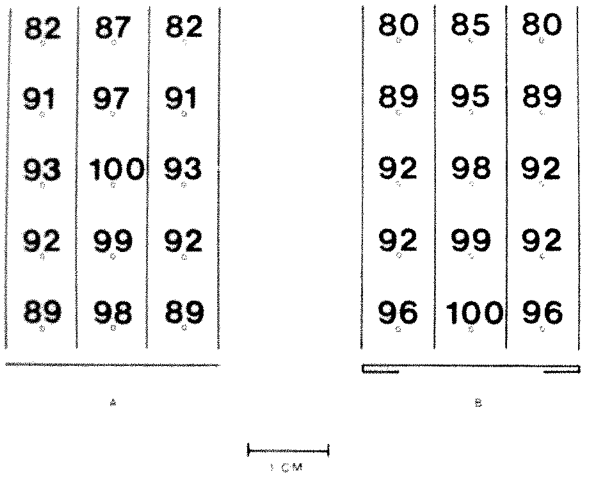

FIG. 6.

Normalized dose distribution 5 mm from the plane of implant showing the effect of bending back ends of crossing wire, (bent back on right, not on left).

reduced operator exposure, radiographic control of implant before insertion of radio-active sources, and ease of removal. In addition it has a number of distinct advantages over the afterloading techniques described before (Pierquin, 1964; Paine, 1972). The accurate positioning of a crossing wire allows the entire dorsum of the tongue to be adequately and reliably treated.

Computer calculations of dose rates show that the 5 mm excess wire bent around at each end of the crossing wires has very little effect on the radiation distribution. In all implants the effect is beneficial (Fig. 6), being more noticeable with smaller implants. It is also found that the best dose on the dorsum of the tongue is obtained when the active ends of the vertical sources are extended as close to the crossing wire as possible (± 2 mm).

Having dispensed with the loop, afterloading the vertical tubes is quick and simple. The time delay between the insertion of the crossing wire and vertical wires produces negligible distortion of the dosage distribution. Calculation shows that even a two-hour delay in a 72-hour implant produces only a 1% increase in the dose at the superior edge of the implant.

As illustrated in Fig. 6, the calculation shows that the tumour is treated effectively only to within 1.5 cm of the uncrossed ends. Swelling of the tongue invariably occurs and often changes the radiation distribution by elevating the sources and consequently underdosing the base of the tumour. One of the main advantages of our method is that it allows and compensates for such swelling. Tissue swelling of 1 cm is allowed for by clamping the nylon balls at this distance from the skin. The active length of the vertical wire is increased by 1.5 cm to prevent a change in radiation dosage distribution over the tumour volume. Thus, to allow for both uncrossed bottom ends and swelling, the active lengths of the vertical wires must extend to at least 2.5 cm below the lower border of the volume to be treated.

This method also minimizes the patient's discomfort and improves oral hygiene during treatment, since there are no tubes protruding into the mouth. A limited amount of tongue movement is possible without danger of dislodging or altering the relative position of radio-active sources; hence oral feeding and limited speech is possible.

It is important to note that polythene tubing must be used for the outer tubing as nylon is not easily pierced. Furthermore, polythene softens in saliva, and the small protrusions are less likely to irritate the palate. Nevertheless, if the patient has an upper dental plate, he is encouraged to wear it to protect the palate from the projecting polythene tubes.

In conclusion, we believe this technique to be an improvement on existing methods. It is reliable, gives good geometry, is simple, and is suitable for all tumours of the tongue and floor of the mouth.

Acknowledgments

We would like to thank the Medical Superintendent, Dr. J. Wessels, for permission to use hospital records for publication: Mr. Harrison for technical help; Mr. S. Leibowitz for the photography; Mrs. D. Smith for typing the manuscript; and the Radiotherapy Special Fund, Provincial Hospital, Port Elizabeth, for financial support.

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Book review

Radiologic Anatomy of the Brain. By G. Salamon and Y. P. Huang, pp. xi + 390, illus., 1976 (Berlin, Heidelberg, New York, Springer-Verlag), $147.60.

This fine book clearly describes the radiological anatomy of the brain with the aid of a well selected series of photographs and radiographs of beautifully prepared cadaver brains, casts, injected specimens and angiograms showing the arterial and venous systems and their distributions. All are labelled or accompanied by diagrams, which makes the work an ideal atlas.

Anatomical variations are discussed and limitations of normality and radiological measurements are quoted. There is a good index and selection of references.

This work is of lasting value. It is a credit to both authors and publishers and it is recommended to all interested in the neurosciences.

B. E. Kendall.

1978, *British Journal of Radiology*, *51*, 218–219

Case report

Solitary neurofibroma of the trachea

By H. C. Meredith, M.B., B.S., M.R.A.C.R., and J. F. Valicenti, Jr., M.D.

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(Received February, 1977 and in revised form June, 1977)

Tracheal tumours are rare and are often missed in plain chest radiographs. This paper is the first recorded example of a tracheal neurofibroma arising from a branch of the vagus nerve.

Case Report

The patient was a 60-year-old white male who, for 18 months, had complained of a substernal wheeze on exertion, exertional dyspnoea and cough, and attacks of acute respiratory distress. There was no haemoptysis or dysphagia and he was treated for bronchial asthma until bronchoscopy revealed the tumour which had not been recognized in plain chest films.

He showed no evidence of a neurofibromatosis and apart from reduction in pulmonary function tests and a PO_2 of 74, his laboratory tests were negative. There was no family history of neurofibromatosis.

He underwent thoracotomy and a smooth rounded pedunculated tumour, 2.5 cm in diameter, arising from the posterior wall of the trachea, 3 cm above the carina was excised. He has had no tumour recurrence.

Discussion

Tracheal tumours are often missed on plain chest radiographs because of their rarity. The röntgenographic aspects have been described in the radiological literature (Fleming, 1962; Huguenin-Dumittan *et al.*, 1969).

This is the first recorded example of an intratracheal neurofibroma arising from a branch of the vagus nerve but three cases of a tracheal schwannoma

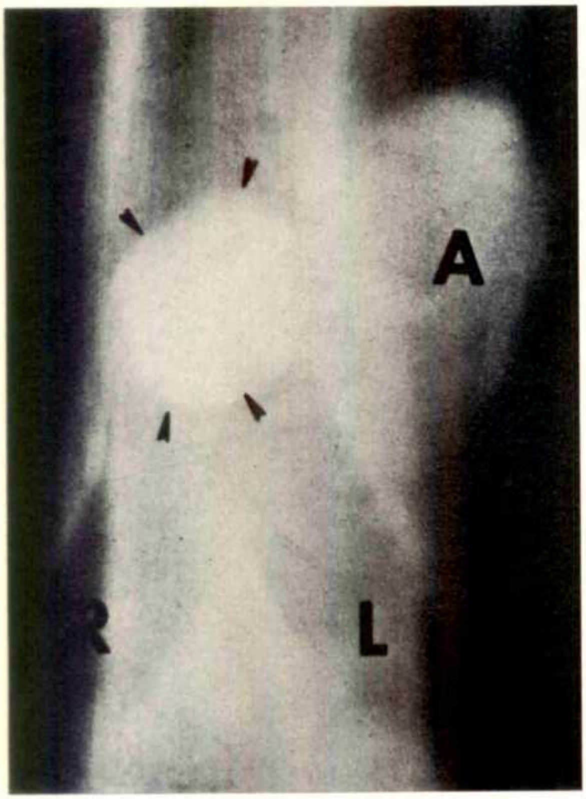

Fig. 1.

Neurofibroma (arrowed) shown in tomograms of distal trachea. A—aortic knuckle R—right bronchus L—left bronchus.

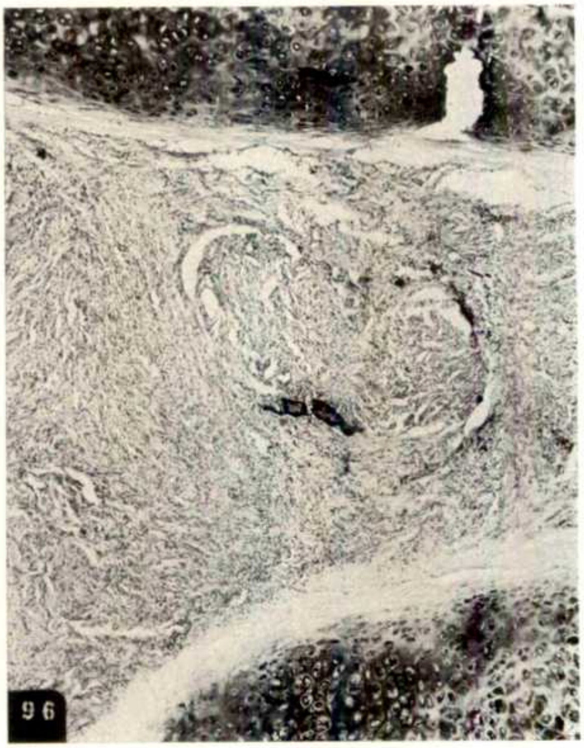

Fig. 2.

The tumour presents between two tracheal rings. Centrally is a large nerve surrounded by perineural space. H&E 40 ×.

(Kittinger, 1961) have been described. These patients were not included in a list of 24 patients reported with tumours of the vagus nerve (Strickland and Wolverson, 1974). None of these tumours were intratracheal but they were located most commonly in the superior mediastinum, more frequently on the left side. In one patient bilateral tumours were present. The pathology of 21 of these tumours was recorded; 14 were neurofibromas and seven schwannomas. Neurofibromatosis was present in eight of the patients with neurofibromas but in none of the patients with schwannomas.

The Schwann cell is the cell of the origin of both schwannomas and neurofibromas. Their separation of morphologic grounds has been suggested (Stout, 1949).

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Book reviews

Dictionary of Medical Ethics. Edited by A. S. Duncan, G. R. Dunstan and R. B. Welbourn, pp. 336, 1977 (London, Darton, Longman and Todd), £4·90.

Can you review a dictionary? The task is not that difficult here, because the editors have in mind not just "a book dealing with words" but also with "information or reference of any subject". Most entries are quite long. The book is written by a galaxy of talent, 116 eminent men and women contributing mini-essays on nearly every conceivable topic. Here is a specimen run of entries: Sexually Transmitted Disease—Shinto—Shock Therapy—Situational Ethics (see "Christianity")—Smoking—Social Workers. The volume is a paperback, almost but not quite pocket size.

Some readers may bemoan the need for publishing such a book at all, pointing to the days when professional ethics was a natural inbred part of every doctor's equipment. Most would probably agree that matters have grown much more complex now that the medical contract is no longer between one patient and one doctor. This book is full of information for seeking a path through the new minefields. The entries generally favour a cool, balanced, middle-of-the-road approach, and do not preach. This is of course all to the good, even if it makes for slightly anaemic reading—perhaps because one's own prejudices are not allowed to the fore. Certain themes recur, for instance that of the hospital as a place for curing disease rather than caring for people. Abortion is another. All entries are signed, and some stand out head and shoulders, like Douglas Black and John Rivers on Resources, which I shall certainly want to read again.

The book makes interesting personal bedside reading, but its most useful place is probably the medical library. It is a good source of information on all sorts of perhaps unexpected subjects, for example the funding of research in this country. Chairmen of Research Ethical Committees may well like a copy as standard stand-by.

Thomas Sherwood.

Roentgenologic diagnosis. Vols. I and II. By J. G. Teplik and M. E. Haskin, pp. 1478, illus., 1976 (W. B. Saunders Co., Sussex), £48·75.

This is the third edition of a two volume (*c.* 1500 pages) radiological book written specifically as a complementary companion to the very popular textbook of medicine by Beeson and McDermott. It is not meant as a radiological text for radiologists but has many worthwhile features.

The first volume contains ten sections and the second nine in the same order as Beeson and McDermott. At the end of the second book a clinically orientated appendix of special roentgenologic procedures is included which is useful but would, I believe, have been more worthwhile had some of the contraindications, untoward reactions and complications of the procedures been discussed.

Each volume has an appendix list of diseases associated with cardinal radiological signs. I am not a believer in lists and one could easily be misled by these which are in alphabetical order, *e.g.* constrictive pericarditis heads the list of diseases associated with an enlarged left atrium. However, they do remind the reader of possible differential diagnoses.

The text is generally succinct and the radiographic illustrations of remarkably good standard. The sensible use of arrows will, I am sure, be very useful to non-radiologists and some radiologists!

All radiologists should encourage their medical colleagues, whether studying or examining for the higher medical examinations, to use this facility whilst reading the companion Textbook of Medicine. It will do them good and may be the only radiological text they will ever read.

For the radiologist the book is interesting and contains many good classic examples. It represents a different approach from our standard textbooks and I enjoyed reading it.

A. B. Ayers.

1978, *British Journal of Radiology*, *51*, 220

Short communications

The RBE of megavoltage photon and electron beams

By P. C. Williams, M.Sc., and J. H. Hendry, Ph.D.

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(*Received September, 1977*)

A recent MRC Working Party (1975) was convened to discuss the relative benefits of electron or photon megavoltage beams for therapy. The discussion arose due to a feeling among many radiotherapists that normal tissues (especially skin) would tolerate higher doses from electron beams (up to 20%) than from photon beams of similar primary energy. This is contrary to physical expectations and to existing biological measurements. It has been suggested that the contradiction may be due to known differences in depth dose distributions and to some tissue inhomogeneities. To clarify the discrepancy between clinical observations on the one hand and biological measurements on the other, further experiments have been performed to measure RBE values for a gross tissue response where the dose distributions have been kept almost identical.

The effects of five types of radiation have been compared. Cobalt 60 γ rays have been used as the reference radiation, and primary electron energies of 3 and 10 MeV were chosen as these are used most commonly at this centre. 4 MV X rays, which have a similar X-ray and secondary electron spectrum to cobalt 60 γ rays, were included to eliminate any possible difference introduced by the use of continuous or pulsed beams. Finally, 300 kV X rays were used to compare with the known clinical RBE of 1.1 for this quality (Greene *et al.*, 1962). The mean dose rate for each radiation type was similar (~200 rad/min), and the dose per pulse for the pulsed radiations was also approximately the same (~0.015 rad/pulse).

Radiation doses were compared for the production of tail necrosis in 50% of mice (the ND_{50}). This assay has been described previously (Hendry *et al.*, 1976). For irradiations with 300 kV X rays and electrons, lead shielding 3 mm thick allowed only a specified length of tail (20 mm or 40 mm) to be irradiated at 5 mm deep in a 10 mm thick Perspex block. With the electron beams, the problem of scattering at the beam edges was allowed for by increasing the unshielded length of tail by 2 5 mm at 10 MeV and by 6.0 mm at 3 MeV. These length corrections were determined by film densitometer measurements, and were calculated at 90% of the dose in the central beam. The corrections are more important for short-length irradiations, and have a minimal effect at 40 mm length which was used in the majority of the experiments. For irradiations with cobalt 60 γ rays and 4 MV X rays, lead shielding 50 mm thick was used, tapered so that the minimum penumbra was produced with the jig 800 mm from the source. The temperature of the jig holding the tails was maintained close to 37°C (extreme range 36–38°C). The dose to the tails in the irradiation jig was measured at each quality with ionization chambers. For the 20 mm length of tail, where the ionization chambers were large compared with the irradiated length, lithium fluoride thermoluminescent dosimetry was used. The dosemeters were calibrated against an ionization chamber at the same radiation quality but with a larger field size.

TABLE I

ND_{50} VALUES AND RATIOS

Primary source		$ND_{50} \pm$ S.E. (rad)	ND_{50} ratio $\pm$S.E. (1/RBE)
Energy	Radiation		
300 kV	X	2820 ± 50	0·91 ± 0·05
1.1 and 1.3 MeV	$\gamma(^{60}Co)$	3100 ± 150	1.00
4 MV	X	3080 ± 210	0.99 ± 0.08
10 MeV	e^-	2970 ± 70	0.96 ± 0.05
3 MeV	e^-	3310 ± 50 *(3160 ± 50)	1.07 ± 0.06 *(1.02 ± 0.06)

*Corrected doses—see text.

At each radiation quality three experiments were performed. In the first a length of approximately 20 mm was irradiated, in the second and third a length of 40 mm was irradiated. The data from these experiments were pooled after the doses to the 20 mm length were corrected to those for 40 mm using measured data for ND_{50} as a function of irradiated length of tail (Hendry, in preparation). In each experiment, groups of six mice were irradiated at four dose levels between 600 rad above and 600 rad below the expected ND_{50}. Thus, after pooling the results from all three experiments, the determination of ND_{50} for each radiation quality was based on the results of irradiating 72 mice.

The results, shown in Table I, are the ND_{50} values for each of the five radiation qualities, and the reciprocal of the RBE quoted as ND_{50}/ND_{50} (cobalt). The value of 0.91 for 300 kV X rays is in agreement with the RBE of 1.1 accepted for clinical practice (Greene *et al.*, 1962). RBE values for megavoltage X rays and 10 MeV electrons are not significantly different from unity. The largest deviation from cobalt 60 γ rays for the megavoltage beams occurs with 3 MeV electrons, and this can be reduced if a systematic uncertainty between electron and photon dosimetry (Williams, 1977; Holt and Kessaris, 1977) is corrected. This error occurs at 3 MeV because incorrectly calculated dose-correction factors are generally used to correct ionization chamber readings to dose values. For 10 MeV electrons, the dose-correction factors are based on measurements and calculations and therefore the error in dosimetry does not occur.

It is concluded that the biological effectiveness of these megavoltage beams does not differ significantly on the data presented, using this gross normal tissue end point. Clinical differences of up to 20% in dose (MRC Working Party, 1975) are more likely to be due to known differences in depth-dose distributions, and to tissue inhomogeneities.

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1978, *British Journal of Radiology*, *51*, 221–222

Short communications

The response of skin to fractionated heat and X rays

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(*Received August, 1977*)

The combination of X rays with raised tissue temperature may be a useful method of treating some types of cancer. At present most information on the topic is for single treatments, but as improved heating methods develop it is likely that treatments may be given in several fractions as is the practice in conventional radiotherapy. It is therefore desirable to understand how cells and tissues respond to fractionated heat and X rays.

When cells *in vitro* are exposed to a combination of heat and X rays the survival curve obtained normally has an increased slope and a reduced shoulder relative to X-ray treatment alone. There is additional evidence from work with X rays at low dose rate that the accumulation and repair of sublethal damage is inhibited by heating (Ben-Hur *et al.*, 1974). However, in some cases heat appears to cause an increase in the extrapolation number of the X-ray survival curve (Loshek, 1976). It is therefore difficult to predict the response of cells and tissues to fractionated treatments with combined heat and X rays.

We have begun an investigation of this problem *in vivo* using the response of the ear (pinna) in the mouse. After irradiation of the ear there is a skin reaction beginning after about 12 days which reaches a peak at about 30 days with subsequent healing. If the ear is also heated the response to X rays is enhanced but there is no qualitative change from the X ray response providing the heat treatments are not sufficiently severe to cause early necrosis, *i.e.* less than 42.5°C for 90 minutes, or equivalent (Law *et al.*, 1978). In our experiments the ear has been heated by immersion in a temperature-controlled water bath (±0.05°C).

Previous experiments have indicated that the effect of heating on the response to X rays is diminished by increasing the time interval between the two treatments and is completely lost by a separation of 24 hours (Law *et al.*, 1977). Based on this result it was felt likely that for daily treatment of combined X rays and heating there would be no residual influence of the heating on the irradiation part of the combined treatment given on the previous or following day.

The aim of our experiment was to measure the thermal enhancement ratio (TER) for different numbers of fractions, given daily. TER is defined as the ratio of the dose of X rays alone to that with heating to produce a given level of damage (Robinson *et al.*, 1974). In our case each heat treatment was 42.5°C for 30 minutes and was completed six minutes before each irradiation.

After treatment with one, two, five or ten daily fractions of X rays alone or combined with heat the skin reactions were scored on an arbitrary scale from one to nine. Scores up to 2.33 are degrees of erythema and above this are levels of desquamation. Further details are given by Law *et al.* (1977) who also showed a direct correspondence between the maximum score and average reaction during ten to 50 days so that either endpoint could be used. Figure 1 shows the dose response curves for maximum skin score both for irradiation alone and for the combination of X rays with heat. From these results the TER was calculated at the level 4, *i.e.* moist desquamation over less than half the outer surface of the pinna. These values are shown in Table I and in Fig. 2. Also shown in Fig.2 are the results from Myers and Field (1977) derived from single dose effects on growing cartilage in the baby rat tail. It is clear that the TER increases with increasing dose per fraction from about 1.25 at 4 Gy to about 1.65 at 20 Gy.

It seems, therefore, that values of TER obtained from single dose experiments may not apply to treatment given in multiple small fractions except at the same level of dose per fraction. Also TER values obtained in different systems may only be comparable at similar radiation dose levels. For example Robinson *et al.* (1974) obtained a TER value of 2.5 for control of a tumour (at about 53 Gy X rays alone) with one of 1.43 for skin reactions (at about 25 Gy) and concluded that there was a therapeutic ratio of 1.75 using hyperthermia (42°C for one hour) in this experimental system. Some of this difference between the TER for tumour and normal tissues may be due simply to the variation in TER with dose level. By a linear extrapolation of the TER values in Fig. 2 the TER at 53 Gy would be about 2.0 compared with 1.7 at 25 Gy giving a ratio of about 1.2. Our experiments were performed with heating at 42.5°C for 30 minutes, which for hyperthermic enhancement of radiation damage is similar in effect to 42.0°C for one hour (Law *et al.*, 1978). Therefore perhaps part of the difference in TER between tumour and normal tissue observed by Robinson *et al.*, (1974) may be accounted for by the variation in TER with dose per fraction.

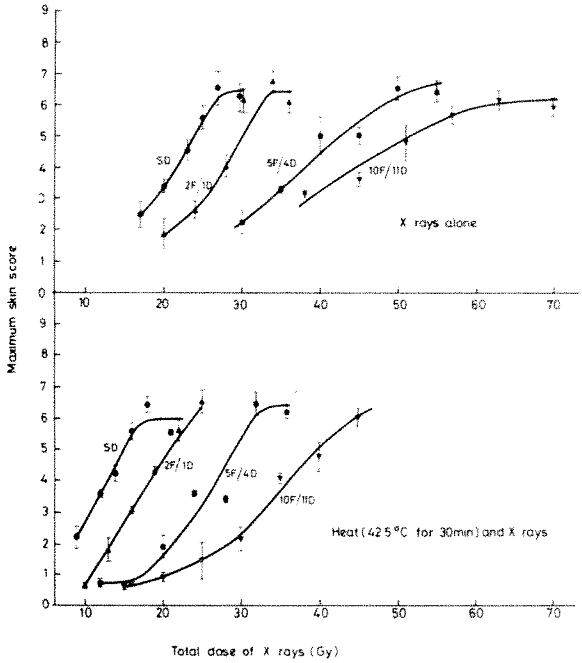

FIG. 1.

The effect of fractionated heat and X rays on the skin of the mouse ear. Upper diagram—X rays alone. Lower diagram—combined heat and X rays. Ears were heated at 42.5°C for 30 minutes immediately before each irradiation. Treatments were given daily: ● single dose, ▲ two fractions, ■ five fractions, ▼ ten fractions. Each point represents the mean for four to six mice and standard errors are shown.

TABLE I

Number of daily fractions	Dose of X rays (Gy)	Dose of X rays with heating (Gy)	TER
1	21.6	13.0	1.66
2	28.0	18.4	1.52
5	38.2	27.0	1.41
10	45.0	36.0	1.25

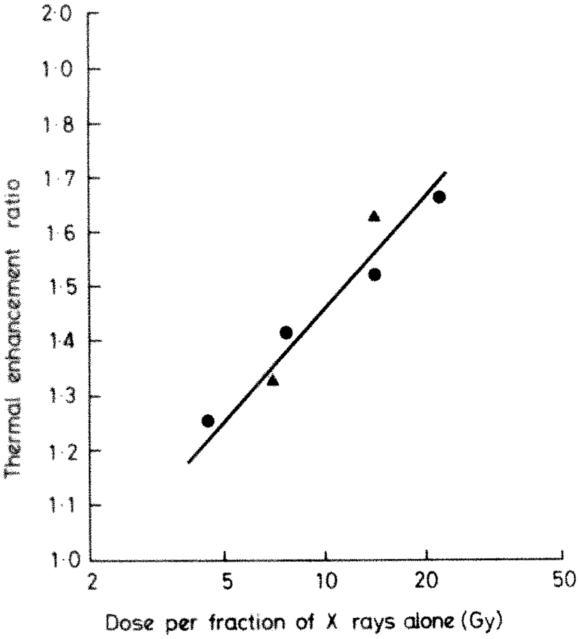

Fig. 2.

The thermal enhancement ratio (TER) for mouse ear skin heated at 42.5°C for 30 minutes immediately before irradiation as a function of dose per fraction. The results are compared with the TER for stunting of the baby rat tail. ● TER for mouse ear skin calculated from data for one, two, five and ten daily fractions. ▲ TER for stunting of the baby rat tail calculated for single doses (from Myers and Field 1977). Heat treatment was 42°C for one hour which is approximately equivalent to 42.5°C for 30 minutes (Law *et al.*, 1978).

The above results may be considered in terms of shapes of survival curves. From Table I, for X rays alone the value of (D_2–D_1) at 24 hours between fractions was 6.4 Gy (where D_1 and D_2 are the doses in a single irradiation or two fractions giving the same reaction). With hyperthermia and radiation (D_2–D_1) was 5.4 Gy. This slight reduction in (D_2–D_1) with heating is consistent with the majority of observations *in vitro* in which the quasi-threshold dose D_Q (Alper *et al.*, 1962) is frequently reduced by combining heat and X rays (Harris *et al.*, 1976; Henle and Leeper, 1977). Thus the major factor in the heat sensitization appears to be an increased slope with a consequent increase in extrapolation number, consistent with the finding of Loshek 1976).

An alternative explanation for the results shown in Fig. 2 is that thermal tolerance is induced by prior heating, as has been demonstrated for heat alone *in vitro* (Gerner *et al.*, 1976; Henle and Leeper, 1976) and *in vivo* (Law *et al.* (unpublished results)). If there were a similar induced tolerance to heat potentiation of radiation damage, then with more than one treatment subsequent heatings would be less effective than the first, depending on the time between doses, giving a reduced TER. If this were the case it would invalidate the survival curve analysis and the TER would depend mainly on the number of fractions rather than the size of each fraction.

Clearly there is much left to understand in this field but the result illustrated in Fig. 2 indicates that the TER may vary with size of dose and fractionation.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

WIDE URETERS, A DILEMMA IN DIAGNOSIS

In his article "Radiology now" Dr. Flower (1977) discusses a subject which is presently the focus of a considerable amount of interest in urological, nuclear medicine and radiological circles, and he rightly emphasises the point that excretion urography in this condition gives a static, anatomical assessment of what is a dynamic situation. However, we would disagree with the statement that "Radioisotope renography often does little more than the urogram in establishing whether there is poor drainage from the kidneys".

In this centre, we have developed a method of diuresis renography which we believe can overcome the inherent disadvantage of simple renography which results in the same pattern in both stasis and true obstruction.

Briefly, a standard ^{131}I-hippuran renogram is performed. A second renogram is performed three minutes after the intravenous injection of 0.5 mg./Kg. of the diuretic Frusemide, which produces a rapid increase in the rate of urine flow.

If the initial renogram remains obstructed at 30 minutes, the diuretic is given while the tracing continues uninterrupted. It has been found that this technique results in one of four possible responses.

Response I	both initial and diuretic renograms are normal, excluding obstruction.
Response II	both initial and diuretic renograms are obstructive, confirming genuine obstruction.
Response IIIa	initial renography is obstructive, but the diuretic renogram is normal. This is the pattern of an atonic, distended but flaccid, non-obstructed upper tract, in which increasing the flow rate allows unimpeded elimination.
Response IIIb	initial renography is obstructive; diuresis results in only a partial improvement in elimination. This is the pattern of a sub-total obstruction.

Thirty-three patients with dilated ureters have been examined by this technique to date. Obstruction has been confirmed in 19. These comprised seven primary megaureters, five patients after ureteric reimplantation, four patients with retroperitoneal fibrosis, two patients with ureteric compression from malignant retroperitoneal nodes and one patient subsequently found to have an obstructing radiolucent ureteric calculus. Surgery has confirmed the obstruction in every case. Obstruction has been excluded in 14. These comprised five patients with persistent ureteric dilatation after reimplantation, four adults with ureterocoele, three patients with ureteric dilatation after ureterolithotomy and two patients with primary megaureter. The response to diuresis can be quantified to give the diuresis excretion index (O'Reilly *et al.*, 1978).

When applied in association with other radiological and radioisotope investigations, the diuresis renogram can make the distinction between stasis and obstruction and thus help to resolve the dilemma of the wide ureter.

Yours, etc.,
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(*In reply*)

THE EDITOR, SIR,

WIDE URETERS, A DILEMMA IN DIAGNOSIS

The technique of Dr. O'Reilly *et al.* is interesting but the interpretation of their results appears to beg certain important questions. It is of fundamental importance to define the term "obstruction". With the perfusion technique, "obstruction" can be defined in terms of a demonstrably increased pressure gradient between renal pelvis and bladder at varying known flow rates. I would ask what evidence they had for obstruction in the 19 cases in which obstruction was confirmed? Did they use a perfusion technique for this confirmation or was it based on visual appearances and the passage of probes, both of which can be extremely misleading?

The technique of renography is concerned with the measurement of isotopic transit time, which is only indirectly related to the presence or absence of obstruction. It depends also on other factors such as renal function, rate of urine flow, patient position and the size and shape of the urinary tract. I am puzzled, therefore, by the conclusions they draw from the use of a diuretic. For example, response III (a) where the initial renogram shows delayed transit but the diuretic renogram is normal, is taken as evidence of a non-obstructed tract. This presupposes that with the increased fluid load provoked by the diuretic, there is no increase in pressure or vis a tergo. I would suggest that there is, and that this increased pressure may allow any obstruction to be overcome.

Yours, etc.,
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THE EDITOR—SIR,

SKIN-SPARING EFFECT IN FAST NEUTRON RADIATION THERAPY

The skin sparing effect in super voltage and telegamma radiotherapy is well known. In the case of fast neutron radiotherapy a similar effect is expected, though to a smaller extent, since the ranges of the secondary charged particles in tissue are smaller. For 14 MeV neutrons, for example, the maximum ranges in tissue of the highest energy secondaries produced in tissue are 2.2 mm (proton), 0.0054 mm (heavy recoil, say, oxygen), 0.134 mm (alpha particle from (n, α_0) event in oxygen). Thus, most of the build up of dose is within a millimetre or two. Further, the skin on the incident field is also exposed to the charged secondaries arising from the (n, alpha) and elastic scattering events taking place in the overlying air. Recent interface dosimetry studies by Bhatia

TABLE I

Depth dose distribution in tissue irradiated with 14 MeV neutrons and the charged secondaries (alphas) arising from the air above the tissue (in units 10^{-10} rad per unit fluence)

Depth in tissue, μm (1)	(n. alpha) contribution from air (2)	Contribution arising in tissue itself				Total inclusive of col. (2) (7)	Ratio (6)/(7)
		(n, alpha) (3)	(n, p) (4)	(heavy recoils) (5)	Total (6)		
20	3.18	11.4	2.86	11.6	25.8	29.0	0.89
25	2.73	11.9	3.9	11.6	26.7	29.5	0.91
30	2.34	12.3	3.72	11.6	27.6	29.9	0.92
35	2.00	12.7	4.10	11.6	28.4	30.4	0.93
40	1.67	13.1	4.48	11.6	29.1	30.8	0.95
45	1.38	13.4	4.84	11.6	29.8	31.2	0.96
50	1.11	13.7	5.21	11.6	30.4	31.6	0.97
55	0.89	13.9	5.57	11.6	31.0	31.9	0.97
60	0.71	14.0	5.92	11.6	31.5	32.2	0.98
2200	0	14.2	50.0	11.6	75.8	75.8	1.0

TABLE II

Estimated surface dose to the skin irradiated by 14 MeV neutrons and covered with a thick layer of air, Al, Sn, Au or Pb* (in units of 10^{-13} rad per unit fluence).

Material	Dose due to† (n, alpha) reaction	Dose due to (n, p)† reaction
Air	7364	1700
Al	4843	3380
Sn‡	10	90
Au	13	16
Pb§	14	6
Tissue	14216	49975

*The values given are the conservative estimates of equilibrium dose. The surface dose (skin dose at zero depth of the skin) would be 50% of the given values for isotropic emission of the charged secondaries and, in no case, would exceed the given values. However, the (n, a) dose from air is the actual surface dose.

†Wherever cross-section is available (n, a) dose is inclusive of (n, ^{3}He), and (n, p) dose is inclusive of (n, d), except in the case of air.

‡For isotopes of Sn with mass numbers 124, 122, 120, 119, 117, 115, 114 (totalling 60% of the natural abundance), (n, a) cross section is not available and hence assumed equal to 0.

§For Pb^{207} (22.6% natural abundance), (n, a) cross section is not available and hence taken equal to 0.

and Nagarajan (1977) have yielded the various components of the skin dose at shallow depths. The components of the dose distributions, of interest to the present discussion, are given in Table I. The depth of the basal layer of the skin would vary from patient to patient. Taking a range of thicknesses of 2 to 5 mg/cm^2 (Harvey, 1971) for the depth of the basal layer of the skin which would be the case for about 50% of the patients, one can readily see from Table I that the air-contribution, in the form of alpha radiation, to the skin dose is about 10% to 5% of the total dose. This total dose, however, is about 40% of the equilibrium dose (or kerma)* which occurs at depths beyond 2 mm. This fraction of the dose (*i.e.* 5 to 10% of the total basal layer dose or 2 to 4% of the equilibrium dose) can be avoided if the alpha particles (and heavy recoils) from the air are stopped by a material that has a low (n, alpha) cross section. Examples of such materials are lead, tin and gold. This reduction in dose would be all the more important as it is from the high-LET component of the dose. The usefulness of a lead filter in reducing the skin dose has been observed clinically (Caterall, 1974).

Table II compares the conservative estimates of the (maximum) surface doses, on irradiation with 14 MeV neutrons, in the cases where skin is covered with a sheet of lead, tin, gold or aluminium and where it is not. The variation of dose with depth contributed by the metal sheets considered was not computed due to paucity of nuclear data. However, it is hoped that the variation would be similar to that of air in Table I. Nevertheless the surface values do indicate the order of reductions that are easily obtainable. Further, it is necessary to keep the metal sheet as close to the skin of the entry beam portal as possible, as it is seen that even small air gaps of the order of a few millimetres would increase the skin dose (Nagarajan and Bhatia, 1977). On the other hand, due to the relatively large (n, p) and (n, alpha) cross sections, a thin aluminium sheet of say a mm or so thickness would increase the skin dose very considerably. The same would be true if the skin is covered with a film of water or any hydrogeneous material, say any locally applied ointment. The above considerations and conclusions would not be applicable for lower energy neutron beams like those of californium 252 fission neutrons or D–D neutrons.

Yours etc.

D. P. Bhatia,

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*In the above discussion only the first collision contribution is considered. The extra dose obtained due to further collisions would be small and, more important, it would be constant over this non-equilibrium region under discussion.

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THE EDITOR—SIR,

WHERE SHOULD A FILM BADGE BE WORN?

Dr. J. Bray in his letter in the July 1977 issue requests the best place to wear the film badge and why.

I advise residents to wear the film badge on their collars outside the lead apron. The film badge is worn to monitor whole body radiation under normal conditions. The NCRP (1968) sets the maximum permissible dose limit for the whole body, gonads, blood forming organs and lens of the eye at 5 rem per year. When the lead apron is worn during fluoroscopy, the lens of the eye is the organ at risk, as the other parts are adequately protected. Wearing the film badge on the collar, or better yet on the side of a scrub cap, gives a better indication of the eye exposure.

I have heard the suggestion that two film badges be worn under those conditions. One under the apron for the whole body exposure and the other at the collar or near the eye for that exposure. I feel that this is unnecessary and generally will lead to bookkeeping problems in maintaining records of exposure.

Yours, etc.,
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THE EDITOR—SIR,

S.I. UNITS

M. F. Docker in his recent letter (1977) about S.I. notation states "although the Americans appear to be especially reluctant, there is no good reason for delaying the introduction of S.I. *wherever possible as soon as possible*".

This typifies the attitude of S.I. protagonists who seem bent on change for (apparently) change's sake.

Has not M. F. Docker considered why the Americans are reluctant? Perhaps they are under less pressure than we have been, and are thus able to consider the wisdom of a change in units in greater depth than we can in Britain.

Surely your correspondent did not mean "wherever possible". As a physicist he is better placed to judge the benefits which may be gained in the physics field, but not in clinical medicine. Radiotherapists have to deal with people, not merely biochemical complexes, and there has been vigorous debate about the introduction of S.I. into clinical medicine (Clark and Sheldon, 1975; Baron, 1975; Bold and Wilding, 1975), suggesting that many are not convinced of S.I.'s "advantages".

The introduction of the gray in deference to the S.I. authorities has obvious dangers when the conversion is by the moving of a decimal point. Already I regret to see it appearing in your journal. My wish is that you will never abandon the rad, to prevent mistakes.

Patients who receive necrotizing doses of radiation as a result of a misplaced decimal point will not be appreciative of the zeal of S.I. protagonists or the system they commend. Any change which complicates patient management (as the gray-rad substitution will), with no benefit to the patient, is to be deplored.

Yours, etc.,
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1978, *British Journal of Radiology*, *51*, 226–232

Proceedings of the British Medical Ultrasonics Group

Abstracts of papers presented at the Eighth Annual Meeting of the British Medical Ultrasonics Group held at Ninewells Hospital, Dundee on December 20 and 21, 1976

The San Francisco meeting, by P. N. T. Wells.
Ultrasonic examination in gynaecology, by A. Kratochwil.
The real-time revolution, by T. A. Whittingham.
The present position of ophthalmic echography, by G. R. Sutherland.
Ultrasonic examination in orthopaedics, by A. Kratochwil.
Grey scale ultrasound diagnosis of pancreatic disease, by H. Meire.
Comparison of a real-time scanning machine with a conventional A- and B- scanning machine, by M. F. Docker.
Echocardiography of cyanotic congenital heart disease with a real-time 60 deg. sector scanner, by A. B. Houston, N. L. Gregory, A. Shaw, D. J. Wheatley and E. N. Coleman.
Mechanical real-time ultrasonic B-scanners for heart and abdominal studies, by W. N. McDicken, C. R. Bow, T. Anderson, G. B. Young and K. Boddy.
Cross-sectional echocardiography in mitral prolapse, by R. A. Lerski, P. Morley and J. C. Rodger.
A doppler ultrasound vascular diagnostic system, by B. A. Coghlan, R. G. Gosling, D. H. King and M. G. Taylor.
Transcutaneous measurement of common carotid artery blood flow using ultrasound, by M. J. Lunt, J. R. Reuben and E. P. G. H. du Boulay.
A comparison of A-scan plus T-M scan and pulsed doppler monitoring of fetal breathing activity, by R. McHugh, W. N. McDicken, K. Boddy and G. B. Young.
An investigation into the accuracy of doppler blood vessel imaging, by P. J. Fish, I. M. Wilson and D. Walters.
Direct measurement of area and perimeter from ultrasonic images, by J. E. E. Fleming, A. J. Hall and B. Wittman.
The ultrasonic estimation of liver volume, by G. Cusick, S. Cusworth, R. J. Blackwell and F. R. Vicary.
Digital processing of ultrasound images, by R. C. Waag, R. Gramiak, P. K. Lee and J. Astheimer.
The internal structure of liver tumours, by T. Bloomberg, D. O. Cosgrove, V. R. McCready and D. H. Rose.
Diffration characterization of tissue using ultrasound, by R. Gramiak, L. P. Hunter, P. P. K. Lee, R. M. Lerner, E. Schenk and R. C. Waag.
Transient sound fields from multi-element arrays, by J. C. Gore and S. Leeman.
An assessment of distortions produced by multi-element arrays, by J. C. Gore, S. Leeman and R. B. Pridie.
Comparison of two methods of constructing multi-element arrays, by M. J. Lunt.
Ultrasonic assessment of fetal renal function, particularly in relation to liquor volume, by J. W. Wladimiroff.
Ultrasonic study on the growth of the placental implantation area in human pregnancy, by K. Vandenberghe.
Estimation of fetal weight, by J. Higginbottom.
Ultrasonic measurements of the placenta: reproducibility and clinical importance, by K. Vandenberghe.
Ultrasonic measurement of fetal head and chest area in relation to fetal growth, by J. W. Wladimiroff.

Reprints of these abstracts are available free on application to the General Secretary, THE BRITISH INSTITUTE OF RADIOLOGY, 32 Welbeck Street, London W1M 7PG, telephone 01-935 6237.

THE SAN FRANCISCO MEETING

By P. N. T. Wells

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This meeting comprised the fifth meeting of the American Society of Ultrasound Technical Specialists, the first meeting of the World Federation of Ultrasound in Medicine and Biology, the Third World Congress of Ultrasonics in Medicine, the Sixth Meeting of SIDUO, and the 21st Meeting of the American Institute of Ultrasound in Medicine. It was held in San Francisco, August 1–7, 1976. A total of 504 papers were presented. There were 56 scientific exhibitors. The opening address, "The Ultrasonic Boom", was delivered by Professor Ian Donald. In this résumé, 11 of the papers were selected for discussion: they dealt with phase cancellation effects, the measurement of ultrasonic attenuation in normal and infarcted myocardium, a phased array sector scanner, a multi-purpose water bath scanner, grey scale display on a bistable tube, the design of a wedged transducer, the relative merits of CT and ultrasonic scanning in abdominal diagnosis, fetal breathing, Doppler evaluation of cerebrovascular disease, hybrid B-scan/Doppler imaging, and ultrasonic CT scanning. Some particularly interesting commercial developments were mentioned. It was decided to hold the Fourth WFUMB in Japan in 1979, the Fifth in Europe in 1982, and the next European Federation meeting in Bologna in 1980.

ULTRASONIC EXAMINATION IN GYNAECOLOGY

By A. Kratochwil

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Because of the variation in anatomy, ultrasonic examination in gynaecology is a greater challenge to the examiner than the application in obstetrics with its well known anatomy.

By studying the echo-anatomy of the female pelvis it has become possible not only to outline and to differentiate gynaecological tumours but also to study physiological changes in the genital organs.

For instance, the growth of the uterus or changes in size during the menstrual cycle can be evaluated.

Of special interest however is the facility to outline maturing follicles in the ovaries during the menstrual cycle and in patients stimulated with hormones.

These examination results are in good correlation with hormone-analytic parameters.

Especially in stimulated cycles, an overstimulation can be detected as early as possible by ultrasonic monitoring of the ovaries.

For the examination of the ovaries a new endoscopic probe to be used during laparoscopy was constructed.

Furthermore, ultrasonic examination in gynaecology forms the basis of exact radiotherapy treatment-planning and for the evaluation of the treatment.

THE REAL-TIME REVOLUTION

By T. A. Whittingham

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A review of the principle methods of producing real-time ultrasonic images for medical diagnosis. Comparison will be drawn between methods based on point by point scanning of the target field and methods in which information from all points in the field is simultaneously detected. The former group of methods includes electronically steered or stepped transducer arrays and mechanical scanning system, while the latter includes the ultrasound camera, holography and digital deconvolution systems.

The benefits and potential developments that high quality, real-time imaging can provide will be discussed.

THE PRESENT POSITION OF OPHTHALMIC ECHOGRAPHY

By G. R. Sutherland

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The paper reviews the development of the use of ultrasound in ophthalmic disorders, concentrating mainly on the application of B-scan systems. The range of pathological processes which can be displayed using the technique were illustrated and the contribution which ultrasound examination makes to clinical management discussed.

ULTRASONIC EXAMINATION IN ORTHOPAEDICS

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The findings of ultrasonic examinations in bone and soft tissue tumours are evaluated for the pre-operative tumour description concerning the size, the border, the structure, as well as the topographic situation.

The results of ultrasonic tomograms are also compared with those of X rays and angiography. It seems that with this simple method a valuable additional examination for diagnosis and therapy of tumours of bone and soft tissues is given which also does not stress the patient.

GREY SCALE ULTRASOUND DIAGNOSIS OF PANCREATIC DISEASE

By H. Meire

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During the past year, 105 patients with suspected pancreatic disease have been examined on a commercial grey scale ultrasound machine (Nuclear Enterprises Diasonograph). To date, full clinical follow-up has been obtained on 40 patients.

The pancreas was successfully visualized in 30 (75%) of the cases with completed follow-up; upper abdominal gas prevented visualization in the remaining 25%. The majority of non-visualized pancreases were clinically normal on follow-up.

In the visualized group with follow-up the correct diagnosis was made by ultrasound in 27 (90%), the diagnostic errors consisting of two false positives and one false negative.

The technique used for pancreatic scanning was discussed and examples of the typical appearances of the normal pancreas and of inflammatory and neoplastic disease was presented.

COMPARISON OF A REAL-TIME SCANNING MACHINE WITH A CONVENTIONAL A- AND B- SCANNING MACHINE

By M. F. Docker

Birmingham Maternity Hospital

It is apparent that dynamic, real-time ultrasound scanning equipment will be used increasingly for obstetric examinations. Standard real-time scanners are not usually provided with A-scan facilities and thus are not capable of such high accuracy when used for measurement. However, the ease with which the mid-line structure can be identified enables quicker and thus more reliable measurement of the fetal biparietal diameter to be made, especially when the fetus is moving. We compared a Kretz-ADR real-time scanner with a Kretz Combison conventional scanner. The results presented demonstrate that measurement was as accurate, as reproducible and quicker with ADR than with Kretz Combison.

The ability to visualize moving structures enhanced the appearance of the display immensely. Fetal movement, breathing, cardiac activity, and cord were readily seen. The ability of the acoustic shadowing by fetal parts to mask the placenta was clearly demonstrated. The real-time scanner would appear to offer an exciting complement to an existing scanner, and a satisfactory substitute where no scanner yet exists.

ECHOCARDIOGRAPHY OF CYANOTIC CONGENITAL HEART DISEASE WITH A REAL-TIME 60 DEG. SECTOR SCANNER

By A. B. Houston, N. L. Gregory, A. Shaw,
D. J. Wheatley and E. N. Coleman

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Department of Clinical Physics and Bio-engineering
Glasgow

A wide angle (60 deg.) mechanical sector scanner producing a real-time two-dimensional echocardiogram has been used to assess great artery anatomy in 28 infants and children with cyanotic congenital heart disease. Longitudinal scans show the relationship of the mitral valve and ventricular septum to the posterior great artery, and transverse scans the spatial relationships of great arteries. In 19 patients the echocardiographic examination was preceded by definitive diagnosis by angiocardiography: ten with transposition of the great arteries showed echocardiographic evidence of parallel great arteries; four with Fallot's tetralogy showed normally related great arteries with an over-riding aorta;

four with double outlet right ventricle had parallel great arteries, but only two clearly showed that both great arteries arose from the right ventricle; one with persistent truncus arteriosus showed a single artery with abnormal cusp echoes. Eight infants and a nine-year-old boy were examined prior to angiography: in all eight infants the echocardiographic assessment closely correlated with that found at angiography; in the other child with corrected transposition the appearance was initially misinterpreted as normally related great arteries. Two-dimensional echocardiography, by providing information which cannot be obtained by other non-invasive techniques, allows better planning of subsequent cardiac catheterization and angiocardiography.

MECHANICAL REAL-TIME ULTRASONIC B-SCANNERS FOR HEART AND ABDOMINAL STUDIES

By W. N. McDicken, C. R. Bow and T. Anderson

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G. B. Young and K. Boddy

Simpson Memorial Maternity Pavilion, Edinburgh

The mechanical approach to real-time B-scanning is discussed in comparison to electronic scanning systems. The requirements of a mechanical scanner are considered such as frame rate, field of view, smoothness of operation and suitability for particular applications. Real-time B-scanners are described for heart and abdominal scanning. These scanners are based on the principle of rotating a standard transducer. Results of their application in heart, abdominal and fetal breathing studies were presented.

CROSS-SECTIONAL ECHOCARDIOGRAPHY IN MITRAL PROLAPSE

By R. A. Lerski, P. Morley and J. C. Rodger

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Multiple beam cross-sectional echocardiograms were recorded in 25 patients with clinical and single beam echocardiographic findings consistent with mitral prolapse.

Cross-sectional scanning demonstrated mitral prolapse in 22 patients and allowed three main groups to be defined. (1) In 14 patients the mitral anterior leaflet was elongated, the chordae to it were slack and it impinged on the interventricular septum in diastole. During systole, in 11 of these patients the anterior leaflet formed an arc in the left atrium, making contact with its posterior wall close to the atrio-ventricular junction, while in three, systolic prolapse was less extensive. (2) In four patients both leaflets appeared elongated; in diastole both were abnormally mobile and in systole both prolapsed. (3) In four patients the anterior leaflet appeared thickened and possibly folded; systolic prolapse was into the upper part of the left atrium.

Some features of the conventional echocardiogram were explained by single element selection from the cross-sectional scans.

Because it demonstrates the extent and direction of mitral prolapse, cross-sectional echocardiography has advantages over the single beam method in the investigation of this disorder.

A DOPPLER ULTRASOUND VASCULAR DIAGNOSTIC SYSTEM

By B. A. Coghlan, R. G. Gosling, D. H. King and M. G. Taylor

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Using two Doppler velocity detectors simultaneously to define the ends of a peripheral arterial segment (usually convenient "pulse" sites), the effects of the segment on waveform shapes can be deduced. With real-time spectrum analysis of the Doppler-shifted velocity signals it is possible to numerately diagnose pathological states such as severe stenosis and block with a classification of collateral. These measurements are non-invasive and repeatable, improving patient management and allowing effects of pharmacological agents and surgical intervention to be followed objectively.

The Doppler velocity detectors are fed to a two channel real-time spectrum analyser (Spectrascribe) and the hard-copy analyser output (or sonogram) is used to obtain the maximum frequency outlines of the two spectra, *i.e.* sonogram waveform using a digitizer and computing calculator (Auto-Graph). From the two sonogram waveforms, the parameters T and PI may be found independently of probe-vessel alignment. Transit time, T, is the time delay between the onset of systolic flow at the two sites (foot to foot time), and pulsatility index, PI, the ratio of maximum excursions of the frequency envelope divided by mean height over the cardiac period (peak to peak/mean). Damping factor $\triangle$ (ratio of proximal to distal PI) and transit time T are normalized using figures for a patent vessel of comparable age, and the systolic pressure measured in the segment under observation. In comparison with arteriography on over two hundred vessel segments, diagnostic threshold values $\triangle n$, Tn, emerge, permitting numerical assessment of vessel segment state.

This system is capable of performing in the presence of many interfering signals such as flow in adjacent vessels, poor signal to noise ratio or radio interference. It may be used in many other ways, *e.g.* stress testing of patients for numerate diagnosis of Raynaud's phenomena and prediction of efficacy of sympathectomy.

The initial outlay and running costs of this system are cost-effective when compared with in-patient expenses for arteriography alone, and other savings accrue whilst patient management improves. At present the commercial production of the equipment is being considered by an international medical equipment manufacturer.

Support for this work has come from various sources, including Servier (UK) Ltd, Niagara Therapy (UK) Ltd, The Wellcome Trust, and British Oxygen Co. Ltd, to whom we are most grateful.

TRANSCUTANEOUS MEASUREMENT OF COMMON CAROTID ARTERY BLOOD FLOW USING ULTRASOUND

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A transcutaneous method for measuring carotid blood flow would be useful in the diagnosis of both carotid artery disease and cerebro-vascular insufficiency. In principle, blood flow can be calculated by combining measurements of blood velocity and vessel diameter, both of which can be made transcutaneously using ultrasound. This paper examines the feasibility and accuracy of this method.

Blood velocity was measured using the Parks 806 directional Doppler. The audio output at two different probe angles was recorded on magnetic tape and subsequently replayed through both a zero crossing detector and a spectral analyser. The performance of the zero crossing detector was assessed by comparison with the spectral analysis. The angle of the probe to the vessel was calculated by comparing the spectra of the two audio signals, and the zero crossing output was then used to measure blood velocity, with an estimated error of 10%.

Artery diameter was measured using a Smith Klein Ekoline 20 which was modified to give linear B scan pictures to aid identification of the artery. A series of measurements made during carotid angiography showed that the diameter could be measured with about 15% error.

The common carotid blood flow of ten patients was measured using these techniques. All patients underwent subsequent angiography. Six were normal and in these the measured flow varied from 4.2 to 7.9 ml s^{-1} (mean 6.2 ml s^{-1}). This agrees with measurements made with the electromagnetic flowmeter. Three patients had mild arterial stenosis and in these the measured flows were 7.8, 7.8 and 9.2 ml s^{-1}. The patient with the largest flow (14.0 ml s^{-1}) had a large parieto-temporal mass. It is unlikely that the large spread is due solely to error in the measurement.

In conclusion, common carotid blood flow can be measured with about 30% error using this technique, and the difference in flow between normal and abnormal patients suggests the method is worth developing.

A COMPARISON OF A-SCAN PLUS T-M SCAN AND PULSED DOPPLER MONITORING OF FETAL BREATHING ACTIVITY

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Initially fetal breathing was detected and monitored using an A-scan unit plus a gated T-M trace. This method is very demanding of the skill and time of the operator since it required a distinct chest or abdominal wall echo always to be present in the gated range. Difficulties associated with the technique were discussed. A pulsed doppler instrument was described which has been developed with a view to monitoring tissue movements within the fetal chest or abdomen. This instrument uses a single crystal 2.5 MHz transducer. A comparison of A-scan plus T-M scan and pulsed doppler recordings of fetal breathing activity were presented. Other possible applications of pulsed doppler ultrasound in obstetrics were discussed.

AN INVESTIGATION INTO THE ACCURACY OF DOPPLER BLOOD VESSEL IMAGING

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Doppler blood flow detectors have been used by a number of workers (Hokanson *et al.*, 1972, Fish, 1975) to image blood vessels transcutaneously. Unfortunately the dimensions of the images generated are determined not only by the blood vessel dimensions but also by the beam or the sampling volume (if a pulsed flow detector is used) dimensions and the doppler signal detection circuitry. In addition, random errors in the image dimensions arise from two main sources. Firstly, as a result of the stochastic nature of the ultrasound signal scattered from blood, the detection of blood flow is governed by a probability function. This means that the system will not detect and image moving blood at some points within a vessel, during a scan of that vessel. Secondly, if the flow detector is a multichannel pulsed instrument then the registration of blood vessel and the multiple flow detection points will vary with the degree of pressure applied to the probe when scanning.

An investigation of the accuracy of doppler blood vessel imaging has been progressing on three fronts. (1) A comparison of results obtained *in vivo* with results obtained using established techniques. (2) A computer modelling of the measurement technique. (3) Measurements *in vitro*.

The results of preliminary work (Day *et al.*, 1976) using the technique to detect leg vein thrombosis in the lower limbs have been encouraging and the results of the computer modelling and measurements *in vitro* have indicated that errors in cross-sectional area measurement of less than 5% in vessels of the order of 8 mm diameter should be achievable.

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*Seconded from G.E.C. Hirst Research Centre, Wembley, Middlesex.

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DIRECT MEASUREMENT OF AREA AND PERIMETER FROM ULTRASONIC IMAGES

By J. E. E. Fleming, A. J. Hall and B. Wittman

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Measurement is an important part of obstetrical ultrasound and increasing attention is being paid to the determination of head/chest areas and perimeters as indices of fetal maturity. The usual methods of measurement use a planimeter and map measurer but such approaches are tedious and potentially subject to error.

A quick and convenient electronic means of area and perimeter measurement has been developed which, in principle, has the accuracy of the electronic caliper found in most B scan equipment. The device utilizes the caliper to produce a marker dot on the screen which is steered round the outline by a joystick control unit. Voltages derived from the unit enable area and perimeter to be electronically calculated and displayed. To facilitate the measurement process a scan converter fitted to an NE 4102 Diasonograph has been adapted for multiple picture storage. Then, for example, head and chest sections may be obtained and the measurements performed at leisure.

Proceedings of the British Medical Ultrasonics Group

THE ULTRASONIC ESTIMATION OF LIVER VOLUME

By G. Cusick, S. Cusworth, R. J. Blackwell and F. R. Vicary

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A measurement of liver volume may be of use in a number of clinical situations. Over the past few years, several workers have shown that an estimate of liver volume may be calculated from sets of ultrasonic scans.

The estimate of volume obtained can only be as accurate or reproducible as the worst step in the path from scan to volume estimate. One source of error is the calculation of area within a section from the outline of that section. This paper described two means of calculating the sectional area, one of which is computationally simple, but subject to considerable errors with complex outlines. The second method described requires more complicated computation, but is not prone to such errors. Using this second technique a consistency of volume estimate better than 3% has been obtained.

Liver volume estimates have been made in a number of normal volunteers. Preliminary data obtained in a study of thalasaemic children will be presented.

DIGITAL PROCESSING OF ULTRASOUND IMAGES

By R. C. Waag, R. Gramiak, P. K. Lee and J. Astheimer

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Digital processing of pulse echo ultrasound data recorded during patient examinations employing moving beams has been applied to improve boundary continuity and definition of structure, to extract time-motion records including those not directly obtainable transcutaneously, and to show spatial and temporal changes in signals from heart structures as they move during the cardiac cycle. Processing is carried out on data that have been arranged in matrices consisting of 256 × 256 points with eight bits of amplitude resolution. Interpolation has been used to produce frames with continuous depiction of structure from a minimum number of ultrasound scan lines, thereby overcoming the constraints imposed on real-time imaging systems which must divide available data according to resolution over angle of scan and frame rate. Signal averaging and peak detection are easily accomplished with the matrix data to eliminate artificial amplitude variations induced by compound scanning of the ultrasonic beam and non-ideal structure illumination. Two-dimensional Fourier transforms have been used to enhance images by applying various filter functions including dc blocking, Laplacian edge detection, and smoothing windows. Sequences of two-dimensional spectra display time variations of cardiac image spatial frequency content throughout the heart cycle. Histograms of signal amplitude have permitted redistributions of echo amplitude for improved grey scale display of small differences. Digital processing of ultrasound data promises to provide new information for non-invasive medical diagnosis of normal and abnormal conditions.

THE INTERNAL STRUCTURE OF LIVER TUMOURS

By T. Bloomberg, D. O. Cosgrove, V. R. McCready and D. H. Rose

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While the accuracy of "B" ultrasound with grey scale in detection of liver metastases has been reported on several occasions and is generally agreed upon, the appearance of these deposits is a matter of controversy. In this series focal metastatic lesions have been studied in an attempt to quantitate the level of echoes returned. This was done by adjusting the signal attenuation to restore the echo levels from the deposit to those produced by surrounding normal liver. A range of ± 10dB was found with a suggestion that the higher echo levels were from deposits of gut origin. When thus compensated most lesions have echo patterns undistinguishable from normal liver.

DIFFRACTION CHARACTERIZATION OF TISSUE USING ULTRASOUND

By R. Gramiak, L. P. Hunter, P. P. K. Lee, R.M.Lerner,E. Schenk and R. C. Waag

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Wave interference has been applied to characterize tissue ultrasonically by measurement of scattered ultrasound intensity as a function of angle and frequency. Data have been collected using a computer-based system which can also control transducer-specimen orientation during the course of experiments. Model studies using diffraction gratings have provided calibration information about beam width and alignment problems and the effects of beam non-uniformity on the ability of the system to measure diffraction. Gratings with spacings ranging from 0.51 to 1.52 mm were studied theoretically and experimentally.

Fourier analysis of experimental data collected with precise transducer alignments and the target in the far field produced results which were within 5% of those predicted by calculations for single scattering from points. Tissue studies have been carried out on specimens obtained at autopsy. The studies established that differences in ultrasound scattering could be detected and hypotheses have been formed to relate alterations in tissue structures as determined microscopically with those observed using ultrasound. Available liver specimens studied ultrasonically were imaged microscopically and characterized according to uniformity of abnormal element distributions, presence of large vessels, amount of connective tissue and lobule size. These characteristics have been used to group specimens with common features for extensive analysis. The capability of determining structure with ultrasound by employing the concepts of wave interference has been demonstrated. *In vitro* studies yield data which appear to show how various disease processes alter tissue structure.

TRANSIENT SOUND FIELDS FROM MULTI-ELEMENT ARRAYS

By J. C. Gore and S. Leeman

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The conventional, continuous wave description of the acoustic sound field from a transducer was shown to be of limited applicability to pulsed arrays. The implications for array design of several interesting and important differences from the continuous wave field were discussed and illustrated by considering the field from a simple two element array. The differences in behaviour between switched and phased arrays was emphasized but shown to have limited consequences in practice. A summary of the techniques that are available to describe realistic sound fields was given.

AN ASSESSMENT OF DISTORTIONS PRODUCED BY MULTI-ELEMENT ARRAYS

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Images of cross-sections through the heart produced by real-time linear scanners, sector scanners and by ECG triggered B scanners, show variations in organ shape which suggest there are systematic distortions associated with each type of scanner. Unlike conventional B scanners, present real time multi-element arrays have wide, diverging sound fields which scan in a fixed geometrical pattern, so that echoes are misplaced in the image and there is no integration of information from compound scanning. Distortions of shape therefore arise and these were demonstrated with examples. It was shown that the severity of such distortions depends not only on the transducer directivity but also on the nature of the reflecting interface. The precise form of the distortion of shapes also depends on the scanning geometry of the system. The characteristics of three real-time linear scanners were compared, and the relevance of distortions particular to these systems to quantitative clinical measurements was discussed.

COMPARISON OF TWO METHODS OF CONSTRUCTING MULTI-ELEMENT ARRAYS

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Real time ultrasonic scanning can be performed using multi-element arrays. The quality of the pictures obtained with this technique is limited by the shape of the ultrasonic beam which depends on the method of construction of the transducer. Multi-element arrays can be made on the one hand from single large piezo electric crystals with the individual elements defined solely by the silvered electrodes, or alternatively from many small crystals each of which is a single element. These two alternatives represent the maximum and minimum mechanical coupling between adjacent elements, and in this paper beam shapes from similar transducers made in these two ways are presented and compared.

The beam shapes were plotted by moving a small ball bearing in the field and measuring the strength of the received echo using a standard A-scan instrument. The results show that the transducer with maximum mechanical coupling had greater sensitivity and gave a narrower beam.

ULTRASONIC ASSESSMENT OF FETAL RENAL FUNCTION, PARTICULARLY IN RELATION TO LIQUOR VOLUME

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The hourly fetal urine production rate (HFUPR) was measured by means of ultrasound. In 189 normal cases, the mean HFUPR varied from 3.3 ml at 25 weeks to 27.4 ml at 40 weeks of gestation. Beyond 40 weeks there appears to be a reduction in HFUPR. Fetal urine production rate depends on the glomerular filtration rate of plasma (GFR) and the percentage tubular reabsorption of water (TRW). GFR was estimated on the basis of the creatinine clearance:

$$\mathrm{GFR} = \frac{\text{creatinine in fetal urine} \times \dfrac{\mathrm{HFUPR}}{60}}{\text{creatinine in cord plasma}}.$$

TRW was calculated from the HFUPR and GFR.

In 25 normal pregnancies between 37 and 42 weeks GFR of plasma varied from 2.0–7.3 ml/min (mean 4.2). This is equivalent to 15.8–58.2 ml/min/1.73m^2 (mean 34.3). TRW varied from 76.2 to 94.9% (mean 89.5).

Fetal urine production and amniotic fluid volume (AFV) were measured in 67 normal pregnancies between 36 and 41 weeks of gestation. No relationship between fetal voiding and AFV was found. Beyond 40 weeks a slight reduction in HFUPR was accompanied by a distinct drop in AFV.

In fetal growth retardation (fetal weight $< 10\%$; $n = 12$), there appears to be a relationship between reduced fetal urine production and oligohydramnios. In 16 cases of diabetes mellitus HFUPR was mostly within the normal range, occasionally even below it. The same was observed in polyhydramnios (AFV > 1500 ml, $n = 13$).

ULTRASONIC STUDY ON THE GROWTH OF THE PLACENTAL IMPLANTATION AREA IN HUMAN PREGNANCY

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Size and growth of the implantation area of the human placenta, and the relation of the placental bed size to the total intra-uterine surface were studied in the course of pregnancy.

From several abdominal scans the diameters of the placental basal plate, of the chorionic plate, and of the base of the segment occupied by the placenta, were measured; the thickness of the placenta and the height of the segment were also assessed. The uterine diameters and the internal uterine circumference were determined as well. By introducing these measurements into two equations, the surface area of the placental implantation site, and the total internal uterine surface were calculated. Reproducibility and accuracy of the method have been evaluated.

A cross-sectional study was made in a group of pregnant women with known gestational age from 12 weeks on. All the measurements were plotted against gestational age; mean values and standard deviations were calculated for each week of pregnancy, and the regression line for each measurement was studied. The relation of the placental bed measurements to the uterine measurements in the course of pregnancy was also examined. A number of subjects are now being re-examined at regular intervals, in order to study the individual placental growth curves. The first results and possible physiological and clinical implications are discussed.

ESTIMATION OF FETAL WEIGHT

By J. Higginbottom

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A method is described to estimate fetal weight using ultrasound. It is based on the assumption that the weight of the fetus or its volume, as the density is approximately one, will be related to the cube of one or more linear dimensions of the fetus. The dimension initially chosen was the fetal trunk circumference at the level of the liver. The circumference can be measured from a polaroid photograph of a B-scan taken transverse to the fetus and correcting for the known magnification. The appearance of the ductus venosus as two parallel lines enables the B-scan images to be made at the correct level on the fetus.

With this technique it was found that in predicting birth-weight the mean error was approximately 100 g and only rarely exceeded 250 g in babies of less than 3500 g. The results were reliable in babies down to 1000 g and *in vitro* experimental work has shown it to be reliable also in abortuses below 500 g.

Above 3500 g much greater errors occurred probably due to the greater variation in fetal shape. To overcome this a multi-factorial method has been developed. The same cubic relationship is used but this time the fetal weight is calculated from the cube of the sum of the trunk circumference, the biparietal diameter and a longitudinal measurement of the fetus. Although at present only 50 birthweights have been predicted by the improved method, the overall accuracy is similar but this time also in the larger babies up to 5000 g birthweight.

A high standard of ultrasound imaging is required but we find that with practice we are able to obtain satisfactory pictures in 90% of cases. The technique usually takes less than ten minutes to perform and thus can be used on a serial or routine basis. It appears that the technique should be useful for the obstetric clinician in monitoring the at-risk pregnancy or in determining the mode of delivery in difficult cases.

ULTRASONIC MEASUREMENTS OF THE PLACENTA: REPRODUCIBILITY AND CLINICAL IMPORTANCE

By K. Vandenberghe

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Several investigators have made ultrasonic measurements of the human placenta *in vivo;* most of this work concerned the thickness of the placenta in its central part. One group studied the placental volume. We introduced measurements of the placental implantation area.

In a group of pregnant women between 12 and 40 weeks the following placental measurements were made: thickness, volume, and implantation area. These data were plotted against gestational age, and the relation of these measurements to the total intrauterine surface and volume was studied. Individual placental and uterine growth curves are now being performed.

The results of this study will be compared with literature data. The reproducibility, and the physiological and possible clinical importance will be discussed.

ULTRASONIC MEASUREMENT OF FETAL HEAD AND CHEST AREA IN RELATION TO FETAL GROWTH

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Consecutive ultrasonic measurement of fetal biparietal diameter (BPD) and fetal chest area was carried out in 303 normal and 164 complicated pregnancies. All ultrasonic measurements were performed on the Diasonograph 4102. Fetal BPD was assessed according to Campbell's method (sound velocity 1600 metres per second). Fetal chest area was assessed immediately caudal to the fetal heart pulsations at right angles to the fetal spine (sound velocity 1540 metres per second).

In three patients ten ultrasonic BPD and in another three patients nine ultrasonic chest measurements were performed within 24 hours on each fetus. In about 95% of the cases an individual measurement of the BPD fell within ± 1.3 mm ($2 \times \text{SD}$) and of the fetal chest area within ± 1.7 cm^2 ($2 \times \text{SD}$) of the expected mean, indicating a high degree of reproducibility.

Normal pregnancy ($n = 303$)

The mean fetal BPD varied from 67.8 mm at 25 weeks to 96.4 mm at 40 weeks' gestation. The mean chest area varied from 31.5 cm^2 at 25 weeks to 89.4 cm^2 at 40 weeks.

Complicated pregnancy ($n = 164$)

When fetal weight was between 5–10% (borderline cases; $n = 47$), BPD and chest area were below the normal range in 34 and 66% of the cases. In small-for-dates (fetal weight $< 5\%$ $n = 37$), this was 54 and 86%, indicating that ultrasonic measurement of fetal chest area provides a much higher pick-up rate of growth retardation as compared with the measurement of BPD. From our head-to-chest ratio curve, the growth-retarded babies appeared to be either symmetrically or asymmetrically small. Signs which could be attributed to vascular placental insufficiency were present in both types of growth retardation.

Finally, in the large-for-dates (fetal weight $> 90\%$; $n = 28$), only the size of the fetal chest seems to indicate the presence of fetal overdevelopment.

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Proceedings of The British Institute of Radiology

New horizons in intensifying screen technology

Abstracts of papers read at a meeting held on May 20, 1977 at the Edward Lewis Theatre, Middlesex Hospital Medical School, London W1

Chairman: Dr. G. M. Ardran
Image requirements from a radiological point of view, by W. B. James.
How can image requirements be defined? by E. T. Henshaw.
Factors affecting speed and noise properties of intensifying screens, by B. M. Moores and Anne Walker.
Methods of evaluating X-ray film-screen combinations, by J. C. Gore and G. R. Hooker.
New horizons in intensifying screen technology, by F. Sanders.
Rare earth screens of Agfa-Gaevert, by R. Bollen.
Fujimex products, by A. J. Carter (*no abstract received*).
Ilford rare earth system, by D. J. Taylor.
Kodak Lanex screens and Ortho-G film, by N. D. Clarke.
Characteristics of Siemens Titan rare earth screens, by G. Michaelson.
Rare earth phospor technology and its applied use in the Trimax system, by J. D. Carroll.
Users' experience: a radiographic view, by Carole Pritchard.
Users' experience: a radiologist's view, by J. G. B. Russell.
Implications for X-ray exposing equipment, by E. F. Bach and H. T. Goodger.

Reprints of these abstracts are available free on application to the Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG, telephone 01–935 6867.

IMAGE REQUIREMENTS FROM A RADIOLOGICAL POINT OF VIEW

By W. B. James

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Many of the physical components of imaging systems can be defined in mathematical terms. Unfortunately such measurements do not characterize the psycho-physical aspects of image detection and interpretation. Our inability to state and to measure these latter processes severely limits our capacity to make a precise statement regarding diagnostic image requirements.

In general, the diagnostic information recorded by a screen-film combination is governed by its ability to register detail—to reproduce faithfully the images of small anatomical structures with maximum sharpness and minimum blurring. Image quality in this sense has three main aspects —*unsharpness, contrast and noise.* The relative importance of these factors is not necessarily the same in different diagnostic situations. For example, the perception of diagnostic information may be mainly sharpness limited, mainly contrast limited or mainly noise limited. Such considerations will clearly affect the choice of recording system.

Recent improvements in intensifying screen manufacture constitute a significant advance if not a major technical breakthrough. In comparison with existing calcium tungstate technology, the advantages are of degree rather than kind, particularly from the point of view of increased speed. Use of the new screens will allow improved resolution for the same exposure, the same resolution for approximately half the exposure and slightly poorer resolution for as little as one-quarter of the exposure.

Increased screen speed also means reduced tube loading which will increase the possibilities for improving geometric sharpness. It will also allow the use of lower output generators.

Side benefits from the introduction of the new screens have been the stimulation of further research on image quality with particular reference to the interface between the recording system and the radiologist, together with recognition that more attention has to be paid to designing recording systems for specific diagnostic tasks.

HOW CAN IMAGE REQUIREMENTS BE DEFINED?

By E. T. Henshaw

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The results of measurements of the speed and gamma of ten rare-earth film-screen combinations were presented together with measurements of their contrast transfer characteristics under scatter and non-scatter conditions. Comparisons in performance were made between all the systems tested and Ilford Fast and Standard screens using Kodak RP54 film. All the tests were carried out over a range from 55 to 110 kV.

The results of subjective tests carried out with 24 radiographers and 11 radiologists using the same film-screen combinations and radiographs of a Temex phantom female abdomen were also presented.

The objective and subjective results were compared and the differences between them briefly discussed.

FACTORS AFFECTING SPEED AND NOISE PROPERTIES OF INTENSIFYING SCREENS

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Factors which contribute to the overall speed of some commercially available intensifying screens are considered and measurements presented which have a direct bearing on the noise properties of film-screen combinations.

The factors considered are: (a) the spectral content of the light emitted by the screens, (b) the attenuation and absorption of X rays in the screen as a function of incident beam quality, (c) the light output from the screens per unit exposure, and (d) the screen light output per unit X-ray absorption.

The light output per unit exposure or the speed of an intensifying screen is influenced by: (i) the screen X-ray absorption, (ii) the phosphor's X ray to light conversion efficiency, and (iii) the screen's light emission properties. The light output per unit absorption enables the joint effect of contributions (ii) and (iii), which represent an effective conversion efficiency, to be assessed separately from (i). It is the intrinsic light output properties represented by the effective conversion efficiency, as distinct from the X-ray absorption properties, which govern the quantum noise properties of intensifying screens. Higher effective conversion efficiency leads to greater quantom noise for use with a given film. All the rare earth phosphors examined had higher effective conversion efficiencies than the calcium tungstate phosphors; consequently the light spectral sensitivity of the film employed with particular screens will play an important role in defining film-screen noise properties.

METHODS OF EVALUATING X-RAY FILM-SCREEN COMBINATIONS

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The various approaches to evaluating radiographic image quality were reviewed and classified as:

(a) Test object method—the radiographer's, radiologist's and physicist's test objects serve different purposes. The information that can be obtained with each type of phantom was summarized, and some of the limitations inherent in this approach were outlined.

(b) Physical measurements—measurements of quantities such as MTF, Wiener spectrum and Hurter–Driffield curves provide much useful information about different film-screen combinations, but several problems remain unresolved about how each property should be specified. A complete system description requires exhaustive measurements, and the interpretation of different characteristics is not straightforward. Expectations of image quality based on these objective measurements often do not correlate well with subjective impressions.

(c) Mathematical modelling of the diagnostic process—theoretical predictions of image quality or detail detectability have been attempted, *e.g.* by using information theory, signal detection theory, or statistical decision theory, but generally such methods require models of visual perception and radiological decision making that are oversimplified or unrealistic. However, they have been used to suggest how isolated measurements such as noise, sharpness and contrast may be combined into single quantities to predict the detectability of simple objects in a radiograph.

(d) Psychophysical techniques—the use of real observers to give responses to controlled visual stimuli appears most promising and overcomes many of the limitations of the test object approach. A number of techniques have been developed, such as ROC analysis, perceptibility curves, and contrast threshold measurements, and the results may usually be expressed quantitatively. A novel method of assessing the detectability of super-threshold objects, using contrast reduction, was described. This method has been further developed to evaluate subjective visual impressions of different types of radiographic noise, and the decrease in perceptibility of objects of different spatial frequency spectra caused by quantum mottle was demonstrated.

NEW HORIZONS IN INTENSIFYING SCREEN TECHNOLOGY

By F. Sanders

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Professor W. C. Röntgen first asked this question in 1896 and Edison came up with the first new horizon with calcium tungstate in that same year.

The validity of this new horizon lies in the "radiological balance", *i.e.* offsetting the complex image quality, together with quantum mottle and sharpness, against speed. The argument for speed is well known and justified, but we should consider the entire imaging speed, not just phosphor speed.

The "radiological balance" should be adjustable for the radiologist not vice versa. This means that the new horizon is not just one phosphor, but a flexible range of imaging system speeds, designed to meet the needs of the radiologist and the type of examination to produce the optimal diagnostic quality with the minimal possible dose at the best return on our investment.

RARE EARTH SCREENS OF AGFA-GEVAERT

By R. Bollen

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The first generation of rare earth phosphors used for screens were mainly emitting in the green range of the light spectrum and these screens were of course employed in combination with appropriate green sensitive radiographic films.

A second generation of rare earth phosphors became available on the market, phosphors that showed a strong emission in the blue range of the spectrum. The advantages of these new radiographic screens are many, both for the manufacturers and for the hospitals.

The rare earth phosphors of the second generation are lanthanum oxybromides, doped with rare earth elements such as terbium, thulium and/or other elements. The conversion efficiency of these phosphors is about 16%. Calcium tungstate has a conversion efficiency of about 4%.

The speed of these new screens is determined by the phosphor itself, the quantity of it in the screen coating and by the composition of the screen layers.

For image quality it is essential to measure for each density level, the MTF value and also the Wiener spectra and the gradient. Also the so-called "perceptibility curves".

It is necessary to examine what other parameters were investigated in order to develop rare earth screens. It was calculated that the blue emitting rare earth screens of Agfa-Gevaert now on the market, show a better signal to noise ratio in the screens themselves than most other screens.

Indeed, the move from green to blue could be done without drawbacks with respect to speed and image quality.

Tables were shown to demonstrate the screen types that Agfa-Gevaert developed and the speed classes obtained in combination with Curix RP1 film and with Medichrome film. The speed class of Universal screen with Curix RP1 film was considered as 100.

Also shown were the experimental preceptibility curves for the combinations of SE2, SE4 and SE6 screens with Curix RP1 film in comparison with that of Cawo Universal screen with Curix RP1 film.

The main advantage of the MR-Screens is their high speed, which on one hand means low patient dose, less motion unsharpness and longer tube life and which, on the other hand opens a lot of possibilities for application of techniques, resulting in diagnostical information gain.

ILFORD RARE EARTH SYSTEM

By D. J. Taylor

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The Ilford rare-earth screen uses the blue-emitting lanthanum oxybromide phosphor. Since this usefully absorbs about twice as much X radiation as a conventional screen, it makes possible a halving of dose without any loss in radiographic quality. To exploit the photographic advantage of using a fine-grain film, and to avoid increasing the perceptability of quantum mottle, the Ilford system comprises the Rapide screen (which is about 4 × faster than fast tungstate) and Rapid E film (which is about half the speed of conventional films like Rapid R type S). Thus consistent exposure reductions of 50% are available, over the 65–100 kV range, with at least equal, and often superior, diagnostic quality. Greater exposure reductions are possible when conventional films are used, albeit then with an inevitable increase in degradation of the image by quantum mottle.

KODAK LANEX SCREENS AND ORTHO-G FILM

By N. D. Clarke

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Rare-earth phosphors have offered the possibilities of decreased exposures because of their high absorption and high conversion efficiency in comparison with calcium tungstate. The phosphor, its method of incorporation into the screens, and the associated film govern the image quality and relative speed achievable. The phosphor is also determined by physical and chemical considerations such as density and stability. These factors led Kodak to employ a mixture of terbium activated gadolinium and lanthanum oxysulphides in an asymmetric screen pair. The screens are green-emitting and the associated film, Ortho-G, is sensitized to this part of the spectrum. This combination has a speed roughly twice that of a conventional RP film in fast tungstate screens, but with similar image quality.

CHARACTERISTICS OF SIEMENS TITAN RARE EARTH SCREENS

By G. Michaelson

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Dose values per unit blackening are illustrated for a range of combinations including Siemens Titan rare earth screens, and the gain to be expected from using these is discussed. Areas of use are outlined as well as the limitations. The importance of quantum mottle and the influence of the developing machine are mentioned. M.T.F. curves for Titan screens compared with conventional ones are shown. How we can exploit the dose reduction to greatest effect is looked at and possible future areas of interest outlined.

RARE EARTH PHOSPHOR TECHNOLOGY AND ITS APPLIED USE IN THE TRIMAX SYSTEM

By J. D. Carroll

3M United Kingdom Limited, London

3M developed Trimax intensifying screens using phosphor materials based upon terbium-activated gadolinium oxysulphide. When used in conjunction with specially sensitized X-ray film emulsions, Trimax XD and XM, dramatic dose reductions can be achieved without any loss of image quality. In fact when using the Trimax system, by adjustments to exposure techniques, dose reductions should be achieved as well as improved image quality, when compared with ordinary RP film in calcium tungstate screens. New screens and films based on Trimax technology were discussed. These have been designed to offer the same advantages in mammography and radiography of the extremities.

USERS' EXPERIENCE: A RADIOGRAPHIC VIEW

By Carole Pritchard

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We have not found one combination suitable for all our work but use several, utilizing the particular qualities offered by each for specific examinations.

Guide for evaluation of a combination: (1) original tests should involve one radiographer only, since muddles seem to occur when several are involved. (2) Using a phantom, make speed, quantum mottle and resolution assessment against routine combination. (3) Make characteristic curves for contrast and speed evaluation. (4) Compare the new combination in a sequence, *e.g.* I.V.P. examination. (5) Use new combination within the specific examination for which it is required.

We have found (1) the length of time required for full evaluation may involve purchasing screens; (2) Kodak's Lanex and 3M's Trimax systems require special safe light filters which make the darkroom much darker than usual; (3) some processors have green warning lights which will fog the green sensitive film; (4) the possibility of mixing combination: (a) blue sensitive film with green emitting screens (b) blue combination mixed; (5) the moving grid mechanism was unable to cope with some of the very small exposure times achievable; (6) rare earth screens are hygroscopic; therefore cut edges for lead inserts must be sealed; (7) because of the hygroscopicity of the screens, soap and water must not be used for cleaning. The correct manufacturers' cleaning agent must be used since one maker's cleaner has dissolved the supercoat of another manufacturer's screens; (8) difficulty with the actinic marker in being able to cope with the wide range of film speeds now used in our department.

Advantages are: (1) reduction in dose to the patient; (2) the use of rare-earth systems may save the expense of higher powered generators; (3) they may be used to overcome tube rating problems; (4) fine focus may be possible instead of broad; (5) the possible elimination of a grid; (6) the greatest advantage is where short exposures are required to eliminate movement unsharpness, *i.e.* geriatric and paediatric departments, theatre and mobile work, where exposure times can be halved.

We are a specialized unit and we use several different combinations; however, I feel that in a busy general department too many different systems would inevitably result in errors.

USERS' EXPERIENCE: A RADIOLOGIST'S VIEW

By J. G. B. Russell

St. Mary's Hospital, Manchester 13

The cost of replacing screens and cassettes for the United Kingdom was assessed at three million pounds, giving an annual cost with a five-year replacement of £600000. However, it was calculated that half this cost is spent annually already on conventional screens and cassettes, so the additional cost would be £300000 annually.

Allowing a 40% reduction in dose with rare earth screens, it was calculated that 600000 man-rad would be avoided annually, giving a cost per man-rad saved of 50p.

1978, *British Journal of Radiology*, *51*, 236–239

A comparison was made with the cost of other methods of avoiding radiation. This showed that for a unit cost, rare earth screens were more than 1000 times more efficient in minimizing radiation exposure than other examples of expenditure on radiation protection.

IMPLICATIONS FOR X-RAY EXPOSING EQUIPMENT

By E. F. Bach

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and H. T. Goodger

GEC Mechanical Equipment Ltd., Wembley
Middlesex

The implications of the advent of rare-earth screens on equipment are looked at, based on their main advantage of saving patient dose, how this benefit can be used to advantage in radiography and how this can affect future requirements. It is doubtful if there will be any simplification of generators leading to cost savings, as the full benefits can be gainfully employed in improving the diagnostic information obtained and still reducing the patient dose. Some areas of specific interest are noted.

Late effects on normal tissues

Abstracts of papers read at the Radiobiology Work-in-Progress meeting held on Friday, November 18, 1977 at the Reid-Knox Hall, Institute House, 32 Welbeck Street, London W1M 7P G*

Limiting normal tissue reactions as seen from the clinicians' viewpoint, by R. J. Berry.
Functional and kinetic changes in the mouse bladder after irradiation, by Fiona Stewart and Juliana Denekamp.
The tolerance of mouse tails to necrosis after repeated X irradiation, by J. H. Hendry.
The role of vascular damage in the development of late radiation effects in pig skin, by J. W. Hopewell, J. L. Foster, Y. Gunn H. M. Moustafa, T. J. S. Patterson, G. Wiernik and C. M. A. Young.
Blood flow changes in surgically traumatized X-irradiated skin, by C. M. A. Young and J. W. Hopewell.
Radiation effects on rat cervical and lumbar spinal cord, by Ann White and Shirley Hornsey.
Ultrastructural studies on radiation-induced mitotic delay, by R. Rowley.
Quantitative changes in rodent lungs after irradiation, by E. L. Travis, B. Voynovich, D. G. Hirst and S. A. Hill.
Lung damage in C57Bl mice following combined chemotherapy and thoracic irradiation, by G. G. Steel, K. Adams and M. J. Peckham.
Labelling studies in irradiated mouse lung, by P. Coultas, R. Ahier and S. B. Field.

LIMITING NORMAL TISSUE REACTIONS AS SEEN FROM THE CLINICIANS' VIEWPOINT

By R. J. Berry

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Acute reactions in normal tissues are only limiting to the radiotherapist when he chooses to make them so! The common practice of daily fractionated treatment over periods of four to six weeks evolved only because it was found empirically that early skin reactions to orthovoltage radiation delivered in such schedules predicted the level of final late damage. This has been used to individualize treatment to the "tolerance" of individual patients. For small numbers of fractions and short overall treatment times, and for excessively long fractionation, severe late normal-tissue reactions can be produced in the absence of any early response.

For the majority of radiation treatments in the supervoltage era the limiting normal tissue response is probably subcutaneous fibrosis and its indicator telangiectasis. The incidence of these complications is not correlated with acute skin reaction, nor predicted by the Ellis NSD or other similar formulations. Sensitive organs limit treatment of tumours in specific sites such as lung, kidney and central nervous system, but perhaps in each of these the limiting complication is still due to vascular damage, stasis and subsequent fibrosis.

Finally, late tumour induction in heavily irradiated sites is a further complication of radiotherapy which should not be totally forgotten. Illustrative examples of moderate and severe late normal tissue damage in skin, connective tissue and specific limiting organs are shown.

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*Reprints of these abstracts are available free on application to the Managing Editor, *British Journal of Radiology*, 32 Welbeck street, London W1M 7PG (01–935 6867)

Proceedings of The British Institute of Radiology

FUNCTIONAL AND KINETIC CHANGES IN THE MOUSE BLADDER AFTER IRRADIATION

By Fiona Stewart and Juliana Denekamp

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The radiation response of mouse bladders, assessed by urination frequency and bladder capacity, has been correlated with histological and proliferative changes.

Female CBA mice were irradiated locally with 1.8 MeV electrons and followed for 18 months after doses of 10–40 gray. The urination frequency of unirradiated mice is remarkably constant over this test period. No increased frequency was seen after any dose up to four months. Between six and 18 months increased frequency was seen after 20–40 Gy. The response occurred earlier after higher doses and was maximal at 12 months. There was some recovery of function in the lower dose groups by 18 months. Clear dose response curves were obtained. The increased frequency at 6–12 months was associated with epithelial denudation and loss of polyploid surface cells. Fibrosis of the deeper layers was not apparent until after 12 months.

At 18 months after irradiation a severe reduction in bladder capacity was demonstrated by inflation under pressure in freshly-killed mice. The reduction in bladder capacity also yielded a clear dose effect relationship.

Proliferation studies using continuous labelling with tritiated thymidine have demonstrated that compensatory proliferation follows the onset of functional damage. The turnover time of the control epidermis is about one year. Three months after irradiation (25 Gy) there is little change, but at nine and 12 months the turnover time has shortened to about one week.

THE TOLERANCE OF MOUSE TAILS TO NECROSIS AFTER REPEATED X IRRADIATION

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The reduction in the "tolerance" dose for the production of tail necrosis in adult mice has been measured in tails which had previously received single or multiple tolerance doses. The major findings are:

(a) Ability of heavily-irradiated and healed tails to tolerate about a further 90% of the first dose confirming previous observations for the tail and for most other skin sites in rodents, but the effect was slightly dependent on the length of tail which had been pre-irradiated.

(b) The above percentage was applicable between six weeks and ten months after the first irradiation.

(c) The tolerance dose was reduced to about 65% of the original at the third irradiation, and this dose (approximately) remained tolerable at the fourth, fifth and sixth irradiation, all delivered at six weeks interval.

(d) Subsequent to seven weeks after the sixth dose, late effects, observed as atrophy of the tail mostly distal to the healed irradiated region, were more prevalent (occurring in ~40% of tails by eight months) than after the first dose ($\leqslant 4\%$ by eight months). These late effects would reduce the tolerance dose further to about 55% of the original dose.

THE ROLE OF VASCULAR DAMAGE IN THE DEVELOPMENT OF LATE RADIATION EFFECTS IN PIG SKIN

By J. W. Hopewell, J. L. Foster, Y. Gunn, H. M. Moustafa, T. J. S. Patterson, G. Wiernik and C. M. A. Young

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If late radiation damage to normal tissues is to be avoided or treated, more information is required about its pathogenesis and there is need for development of early indicators of severe late effects. The skin, which is ideally suited to a wide range of investigative techniques, would appear to be a good model in which to evaluate this problem.

In the first three to four months after irradiation of pig skin two distinct waves of radiation response are observed. In the first wave, which reaches a peak four to six weeks after treatment, erythema may be associated with desquamation of the epidermis if the total dose is sufficiently high. Provided the epithelium is not seriously denuded this will rapidly heal. The second wave of reaction observed three to four months after irradiation seems to be mediated through damage to the vascular system. It is characterized by a blue tinge to the skin, a reduction in skin temperature and a dose dependent reduction in dermal blood flow. The reduction in blood flow is transient, and blood flow returns to normal as late tissue atrophy develops.

If the ischemia is sufficiently severe it can result in a complete or partial thickness necrosis of the dermis. When the ischemic reaction is insufficient to produce necrosis it seems likely that this may lead to late tissue atrophy. There was a good correlation between the reduction in blood flow at three months (as measured by isotope clearance) and the degree of tissue atrophy (as measured by linear field contraction) 6–12 months after irradiation. Histological investigations undertaken three months after irradiation show evidence of vascular occlusions; arterioles in the deep dermal plexus in particular were totally or partly occluded by increased numbers of endothelial cells.

In the acute radiation reaction, fractionation of irradiation changes the relative importance of the first wave of epithelial reaction as compared with the later vascular response. When single doses or a small number of fractions are used the vascular lesion limits the dose that can be given and causes dermal necrosis with no previous desquamation. With a large number of fractions the reverse is true and epithelial effects limit the dose. Consequently there was no correlation between the presence of moist desquamation in the first wave of reaction and late tissue damage as has been claimed as a result of a number of investigations in rodents. Comparable changes to those found in pig skin have been found in human skin after radiotherapy treatment.

BLOOD FLOW CHANGES IN SURGICALLY TRAUMATIZED X-IRRADIATED SKIN

By C. M. A. Young and J. W. Hopewell

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An isotope clearance technique has been used to determine changes in capillary blood flow in the dermis after surgery, irradiation, or surgery after irradiation in the flank skin of the pig.

Blood flow was indicated by the rate at which a tracer (^{99}Tc^{m}) was removed from the site of an intradermal injection. Clearance curves could be divided into a fast and a slow component. These components are due respectively to clearance by the superficial capillary network and the deeper, less well vascularized parts of the dermis. The distinction between the two components was demonstrated by observing the clearance of deep and superficial intradermal injections of the tracer. The fast component and the vascular density in the superficial capillary network under the epidermis do not change with age. The slow component, however, increased with age and showed a good correlation with the decline in vascularity in the deep reticular dermis over the same time period.

Blood flow measurements were made in irradiated skin at intervals of three, 12 and 24 months after treatment with either a single dose (2130 rad), six fractions in 18 days (3876 rad) or 30 fractions in 39 days (8000 rad), these total doses giving a similar degree of late linear field contraction at 6–12 months. Blood flow was reduced three months after irradiation but had returned to normal by 12 months. The timing of the improvement in blood flow corresponded with the development of late field contraction.

Pedicle flaps were raised from irradiated areas of skin at three, 12 and 24 months after treatment. Blood flow measurements in these flaps were compared with those in skin flaps raised on the normal flank. In normal skin flaps there was an initial fall which was followed by a marked increase in blood flow, suggestive of an hyperaemic response. In irradiated flaps the initial impairment and subsequent increase in blood flow was greater than in control flaps. This indicates that the vascular system of an irradiated flap can apparently mount a greater hyperaemic response than that seen in a normal flap.

RADIATION EFFECTS ON RAT CERVICAL AND LUMBAR SPINAL CORD

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Experiments have been carried out to determine how the dose of 250 kV X radiation which the rat spinal cord will tolerate varies with fractionation and overall treatment time. The effects of varying the overall treatment time independently of the number of fractions were investigated by giving two equal doses of irradiation to the lumbar or cervical region, separated by periods of time ranging from one to 120 days. The patterns of recovery from irradiation damage in both regions were very similar but differed from those reported recently by van der Kogel (1978). During the first 24 hours after irradiation a very large amount of recovery took place. This rapid phase of recovery probably reflects Elkind repair of sublethal damage. No further recovery occurred for about 15 days and then a second wave of recovery, possibly due to replacement of damaged cells by mitosis, appeared to be underway. In the cervical region this phase continued until at least 120 days after irradiation. In van der Kogel's experiments this second phase of recovery did not start until eight to ten weeks. The similarity between the lumbar and cervical regions was surprising because, histologically, the damage in the two regions is very different. Loss of myelin from the spinal roots was the most important lesion in the lumbar region whereas in the cervical region large necrotic areas appeared in the white matter of the cord itself.

The effects of varying the number of fractions whilst keeping the overall treatment time constant were investigated by exposing the lumbar cord to either four, eight, 15 or 30 equal fractions in six weeks. The sparing effect as the number of fractions was increased was very large. Furthermore, the rate of increase of the tolerance dose was the same from one right up to 30 fractions, in contrast to the lung where sparing becomes relatively less between eight and 30 fractions (Field *et al.*, 1976).

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ULTRASTRUCTURAL STUDIES ON RADIATION-INDUCED MITOTIC DELAY

By R. Rowley

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The literature on radiation induced mitotic delay in G_2 indicates that the target whose disruption by radiation causes delay is:

(1) possibly a protein;
(2) located in or near the nucleus;
(3) possibly a structural component of the cell;
(4) at a maximum size of about 1.5 μm in G_2 just prior to the X-ray transition point for induction of delay.

These qualities suggest that an ultrastructural investigation to identify and locate the mitotic delay target may be worthwhile.

We have examined the effects of UV and X irradiation on the cell cycle and ultrastructure of synchronously growing *Oedogonium cardiacum* sporelings. All sporelings were irradiated at 12 h after attachment, i.e. in G_2, fixed in glutaraldehyde and osmium tetroxide, embedded and serially sectioned in their entirety. A 200 erg mm^{-2} dose of 254 nm UV, sufficient to produce 5% loss of reproductive integrity, causes premature chromatin condensation, confirmed by electron microscopy, and induces the early onset of mitosis proper. 1000 erg mm^{-2} UV (69% survival) UV delays sporeling entry into mitosis by 2 h. 500 erg mm^{-2} (74% survival) has an intermediate effect in producing no delay. Apart from this effect upon chromatin condensation no other changes can be detected by electron microscopy that might be correlated with acceleration into mitosis or mitotic delay. It is suggested that the action of UV may be analogous to that of actinomycin D and cordycepin, which produce similar effects in Chinese hamster ovary cells. Both of these chemicals and UV are potent inhibitors of transcription. The ways by which transcription inhibitors might stimulate or delay entry into mitosis are described in Dewey and Highfield (1976).

The specific effect of UV upon both chromatin condensation and mitosis is considered to lend further weight to the proposals of Dewey and Highfield that the substance(s) controlling the onset of mitosis and perhaps also receiving the lesions that cause mitotic delay are closely associated with the chromatin condensation mechanism.

An X-ray dose of 600 rad (producing approximately 60% survival) was chosen for this study using the findings of Horsley *et al.*, (1967). This dose causes maximum delay without totally inhibiting either mitosis or division.

Approximately 200 cells were serially sectioned at various points in the cell cycle, before and after irradiation. Particular attention was paid to the behaviour of the chromatin, nucleolus, nuclear envelope, microtubules, microfilaments, microtubule organising centres and mitachondria. The outcome of this study is that there are no qualitative or quantitative changes in the sporeling observable by this technique that might be correlated with mitotic delay.

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QUANTITATIVE CHANGES IN RODENT LUNGS AFTER IRRADIATION

By E. L. Travis, B. Voynovich, D. G. Hirst and S. A. Hill

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Pulmonary radiation injury in mice is most often quantitated by lethality. There are few other quantitative assays, particularly of functional parameters. In the present study the respiratory rate of mice was measured in a total body plethysmograph up to 24 weeks after total thoracic irradiation with single doses ranging from eight to 20 Gy.

Respiratory rate was increased after doses greater than 13 Gy. This increase was both time and dose dependent, yielding dose response curves. The response was progressive after 16 and 20 Gy, increased but non-progressive after 13 Gy, and transiently increased after 11 Gy. Respiratory rate was used to measure Elkind repair, the dose response curves at 16 weeks yielding a (D_2-D_1) of 410 rad. This value is consistent with the reported (D_2-D_1) of 360 rad using lethality as an end-point.

The changes in breathing rate were correlated with histological changes. A numerical scoring system quantitating the infiltrative, oedematous and fibrotic lesions in the lung after irradiation yields dose response curves similar to those obtained using breathing rate. A preliminary (D_2-D_1) obtained from the histological scoring ranged from 360 to 410 rad, consistent with the (D_2-D_1) using rate and lethality as end-points.

LUNG DAMAGE IN C57BL MICE FOLLOWING COMBINED CHEMOTHERAPY AND THORACIC IRRADIATION

By G. G. Steel, K. Adams and M. J. Peckham

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Male C57Bl mice were treated with local thoracic irradiation at dose levels ranging from 12 to 19 Gy. The irradiations were performed in air at controlled temperature under nembutal anaesthesia. Two sizes of trapezoidal fields were used, varying in the position of the lower (abdominal) border. Deaths occurred earlier with the large fields but the difference in the median day of death was only about 10%. With large fields and using the highest radiation dose the median day of death was 210 days, much later than has been found by T. L. Phillips and others. Chemotherapy was given to mice treated with the smaller radiation fields to a dose of 15.5 Gy. Methotrexate, vinblastine, and actinomycin D given 14 days before irradiation had little effect on mortality, but bleomycin and adriamycin showed some enhancement of damage. Cyclophosphamide given a few hours before or a few hours after irradiation also enhanced lung damage.

LABELLING STUDIES IN IRRADIATED MOUSE LUNG

By P. Coultas, R. Ahier and S. B. Field

MRC Cyclotron Unit
Hammersmith Hospital, London W12 0HS

The LD50 assay of Phillips and co-workers for radiation-induced lung damage has been used by Field and Hornsey (1977) to study the effects of dose fractionation. For two doses of both X rays and neutrons there was an increase in LD50 when doses were separated by a few hours: this was equated with repair of sublethal damage. With longer dose separation beyond one day, no further increase in LD50 was seen for neutrons whereas with X rays the LD50 continued to increase with dose separation up to about 1000 hours. It was postulated that this change in LD50 seen with longer intervals between X ray doses was due to some form of slow repair process, although the possibility of cellular proliferation was not entirely ruled out.

The study we report here was carried out to examine the possibility of a proliferative response to lung irradiation. Mice were irradiated with 10 Gy of 250 kV X rays to both lungs and then injected with ^{3}H-thymidine (0.5 μCi/gm body weight) at eight hour intervals. Injections were started for one group of mice two days post-irradiation and for a second group five weeks post-irradiation. Cell labelling in alveolar areas was examined in autoradiographs. Particular attention was paid to Type II pneumonocytes. These cells have been suggested as a possible critical target in radiation damage to lung, and we support this suggestion with the observation that the numbers of Type II cells are falling rapidly at the time mice die of lung damage. Labelling of Type II pneumonocytes was low in both irradiated and control groups with no apparent differences between the groups. This suggests that if Type II cells are the prime target then proliferation is not a cause of the long term recovery between separated X-ray doses. Overall labelling in the alveolar region did show a slight, but at this stage not significant, increase between both irradiated groups of animals and the controls.

REFERENCE

Field, S. B., and Hornsey, S., 1977. Slow repair after X rays and fast neutrons. *British Journal of Radiology*, *50*, 600–601.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *B.I.R. BULLETIN* which is distributed quarterly to all members.

RECENT ADVANCES IN HYPERTHERMIA RESEARCH

A radiobiology meeting will be held on May 11–12, 1978. Titles of papers on technical, biological or clinical aspects of the topic are invited and should be sent to Dr. S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, London W12 0HS not later than April 14, 1978.

Further information from the General Secretary, B.I.R. (01–935 6237).

COMPARISON OF DIAGNOSTIC TECHNIQUES FOR THE CHEST AND MEDIASTINUM

An evening meeting will be held on March 16, 1978 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Details and registration from the General Secretary.

B.I.R. ANNUAL CONGRESS JOINT MEETING AND SCIENTIFIC EXHIBITION 1978

The Annual Congress will include a joint meeting with the Royal College of Radiologists, the Royal Society of Medicine (Section of Radiology) and the Netherlands Radiological Societies, and will be held at the R.I.B.A., London, W.1 on April 13–14, 1978. Details from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

The "SILVANUS THOMPSON MEMORIAL LECTURE" will be delivered at this congress by Sir John Hill, Chairman U.K.A.E.A. under the title "Nuclear Power and the Environment".

SECOND CONGRESS OF THE EUROPEAN SOCIETY OF NUCLEAR MEDICINE

The Institute and other UK members of the European Society of Nuclear Medicine will be hosts to this congress to be held in London, April 17–18, 1978. The meeting will include a commercial exhibition, scientific demonstrations and technologists sessions.

Further information from the General Secretary B.I.R.

B.I.R. CONVERSAZIONE

Will be held at Northwick Park Hospital, Middlesex on May 17, 1978. Dr. Louis Kreel will arrange demonstrations and give a talk "Introducing art into radiology".

Details from the General Secretary.

HIGH DOSE RATE AFTERLOADING GYNAECOLOGICAL IRRADIATION AS AN ADJUVANT TO GYNAECOLOGICAL SURGERY: AN ASSESSMENT OF THE CATHETRON

An evening meeting will be held on May 18, 1978 at The British Institute of Radiology (Reid-Knox Hall), 32 Welbeck Street, London W1M 7PG.

Further details from the General Secretary.

BENIGN BONE DISEASE–ROLE OF RADIOISOTOPE TECHNIQUES

A joint meeting of the British Orthopaedic Association and The British Institute of Radiology, will be held on May 31, 1978 at the Middlesex Hospital Medical School, London.

WORKSHOP ON THE USE OF COMPUTERIZED TOMOGRAPHIC SCANNERS IN RADIOTHERAPY

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proferred papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

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April 1978

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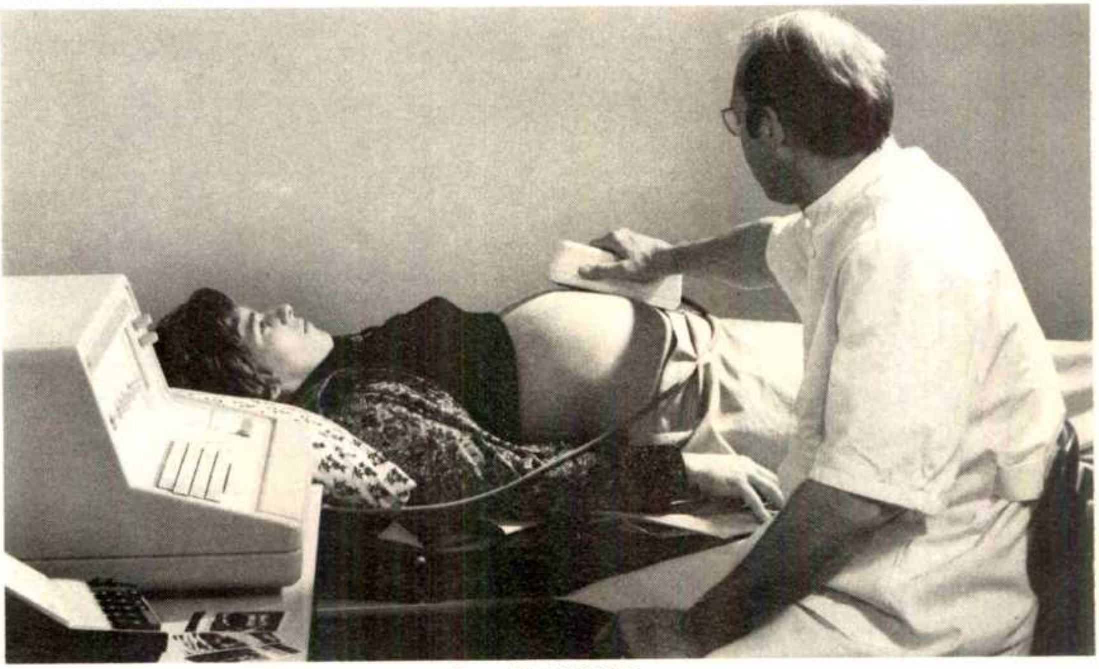

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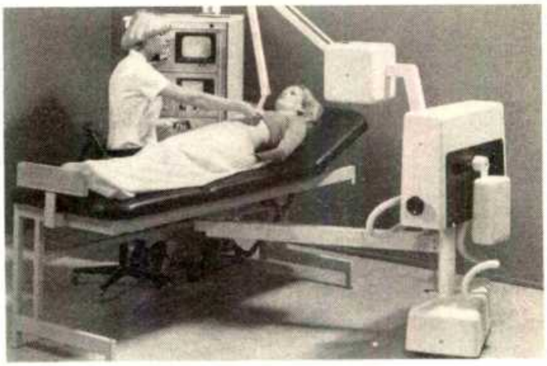

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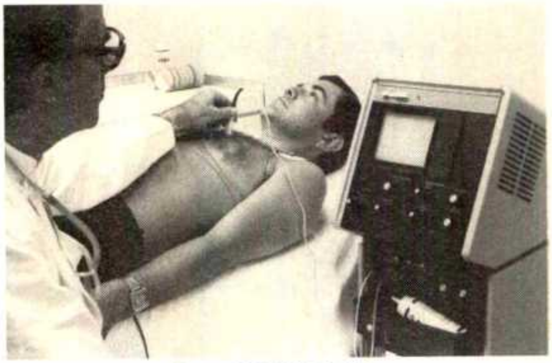

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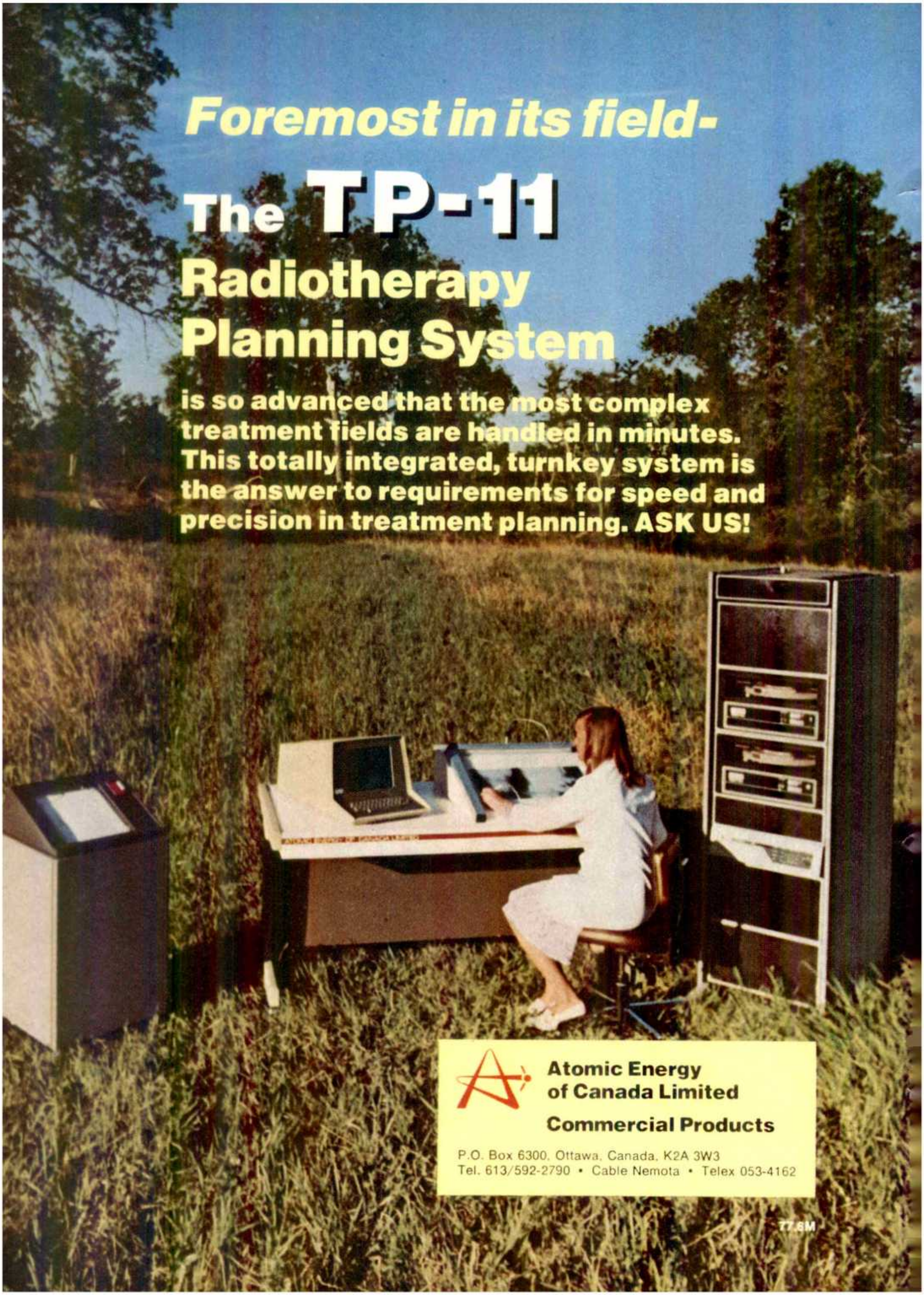

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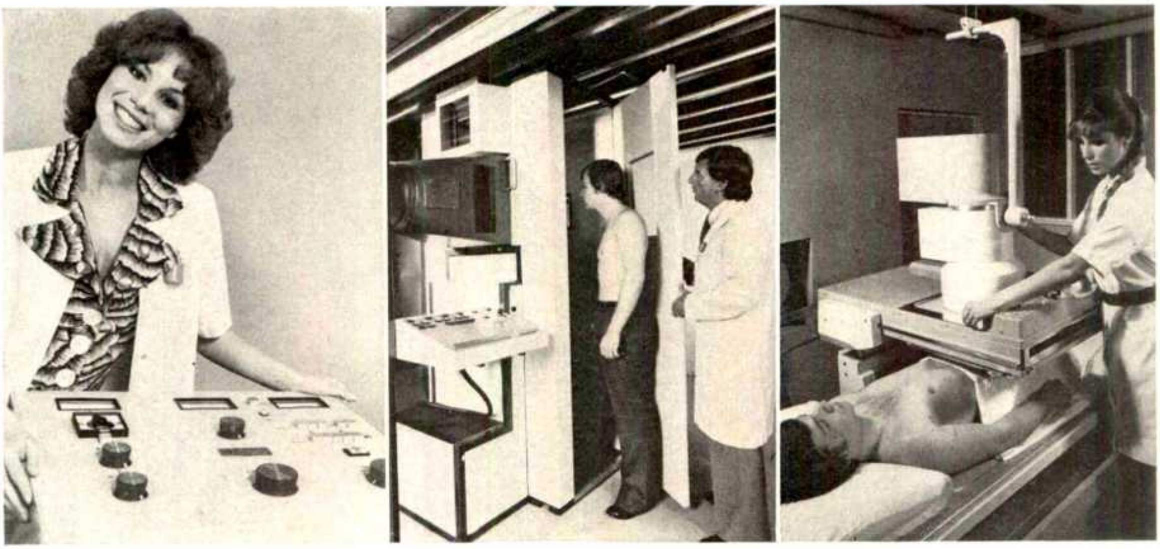

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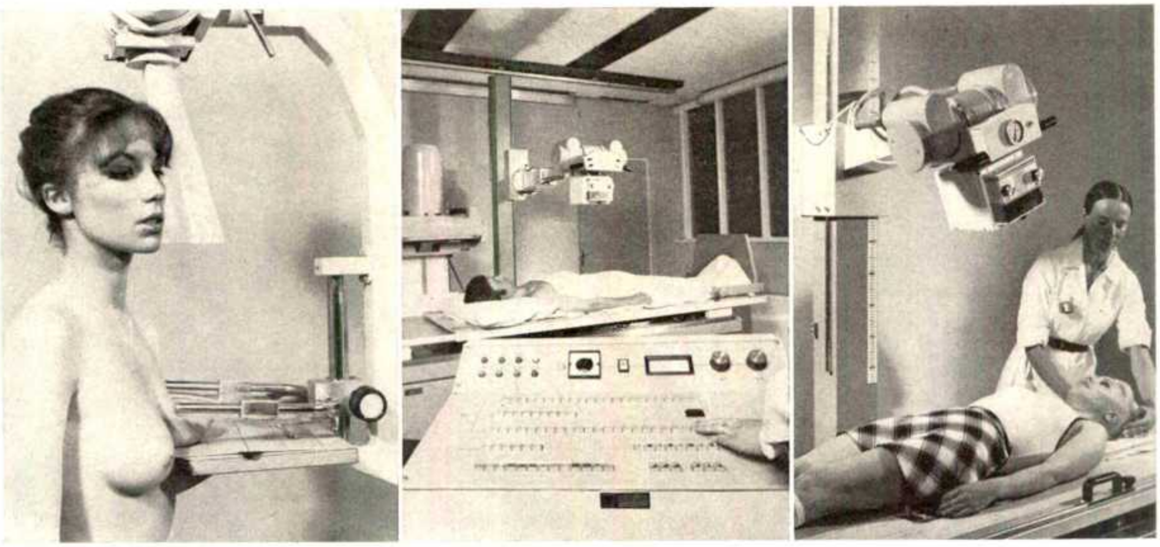

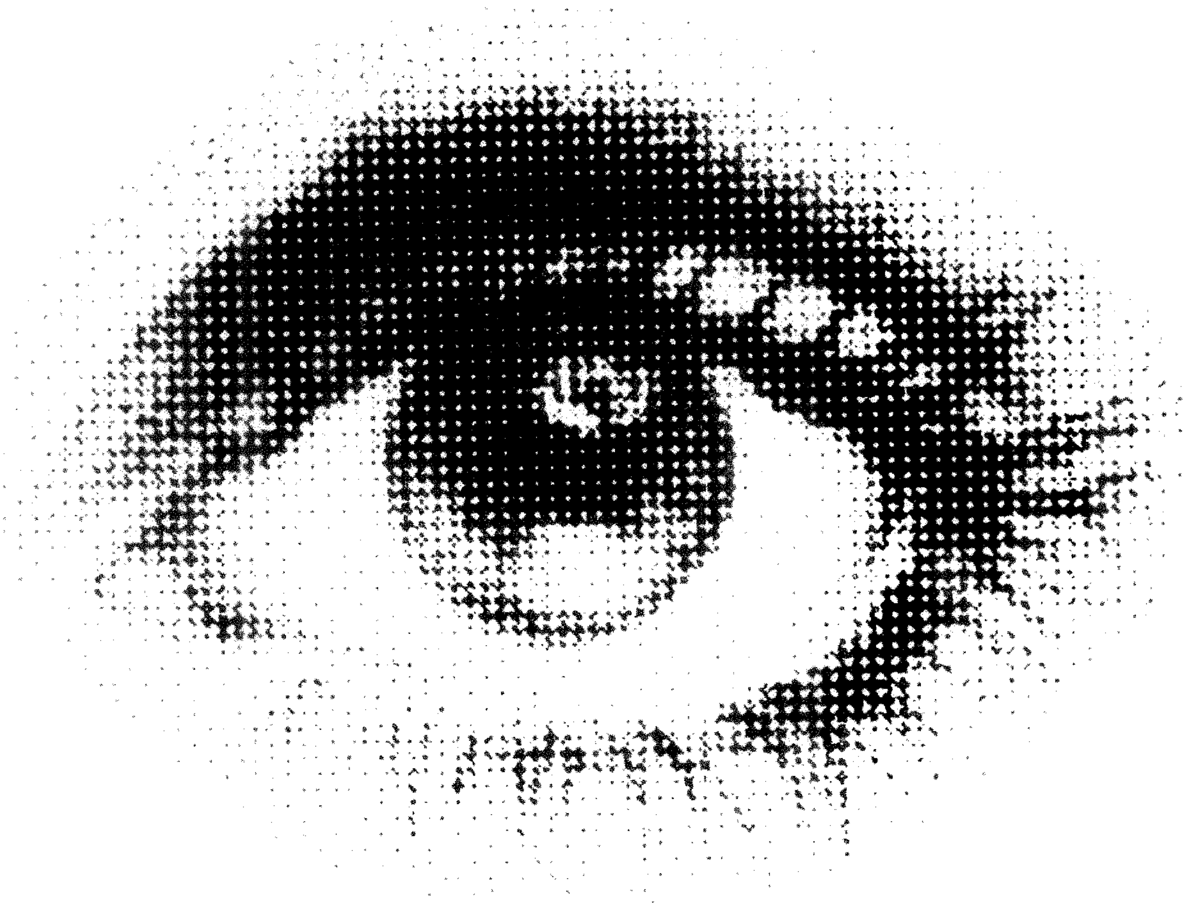

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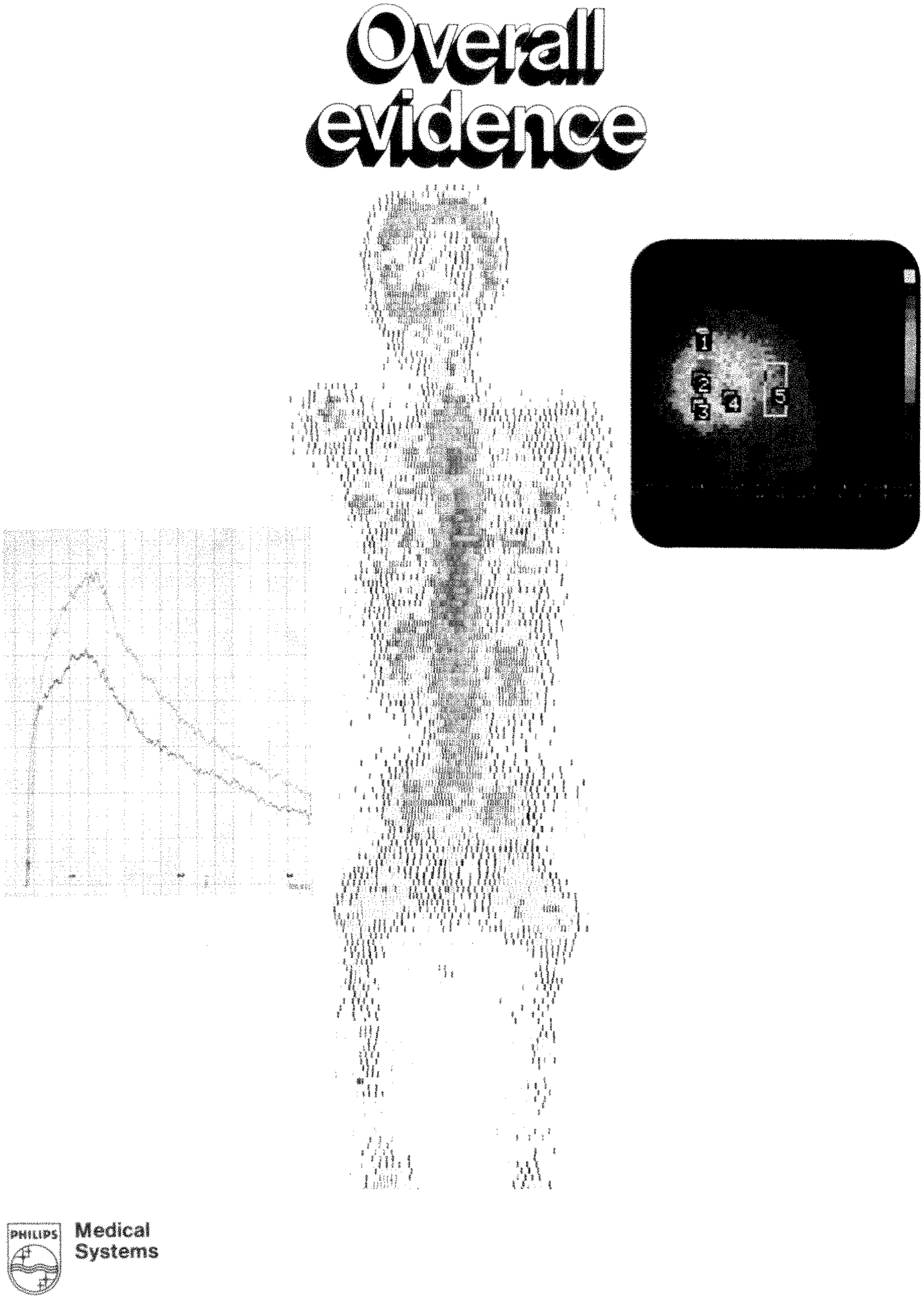
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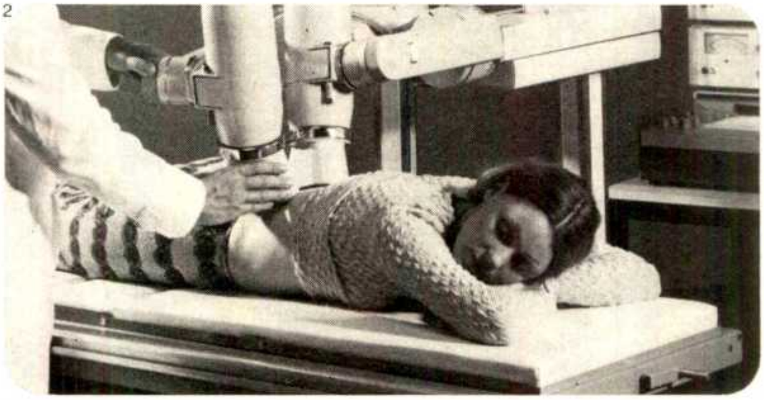

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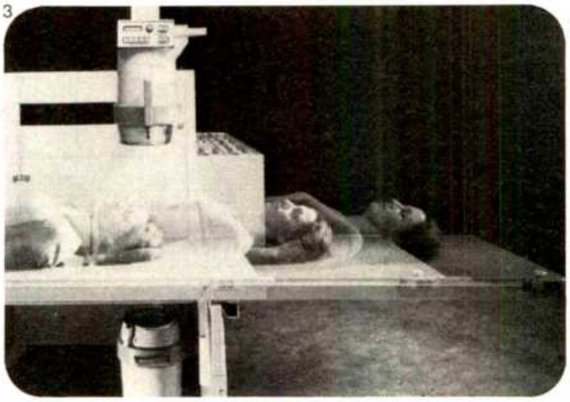

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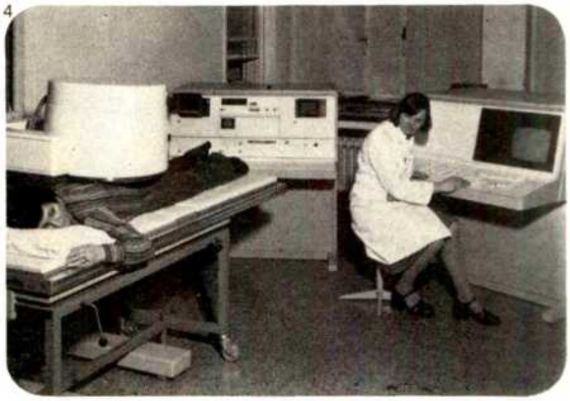

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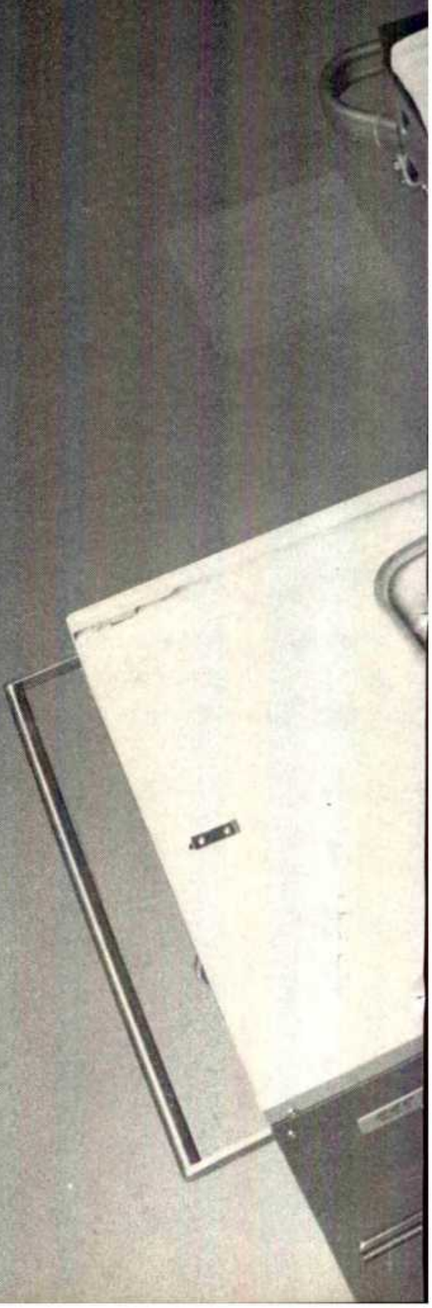

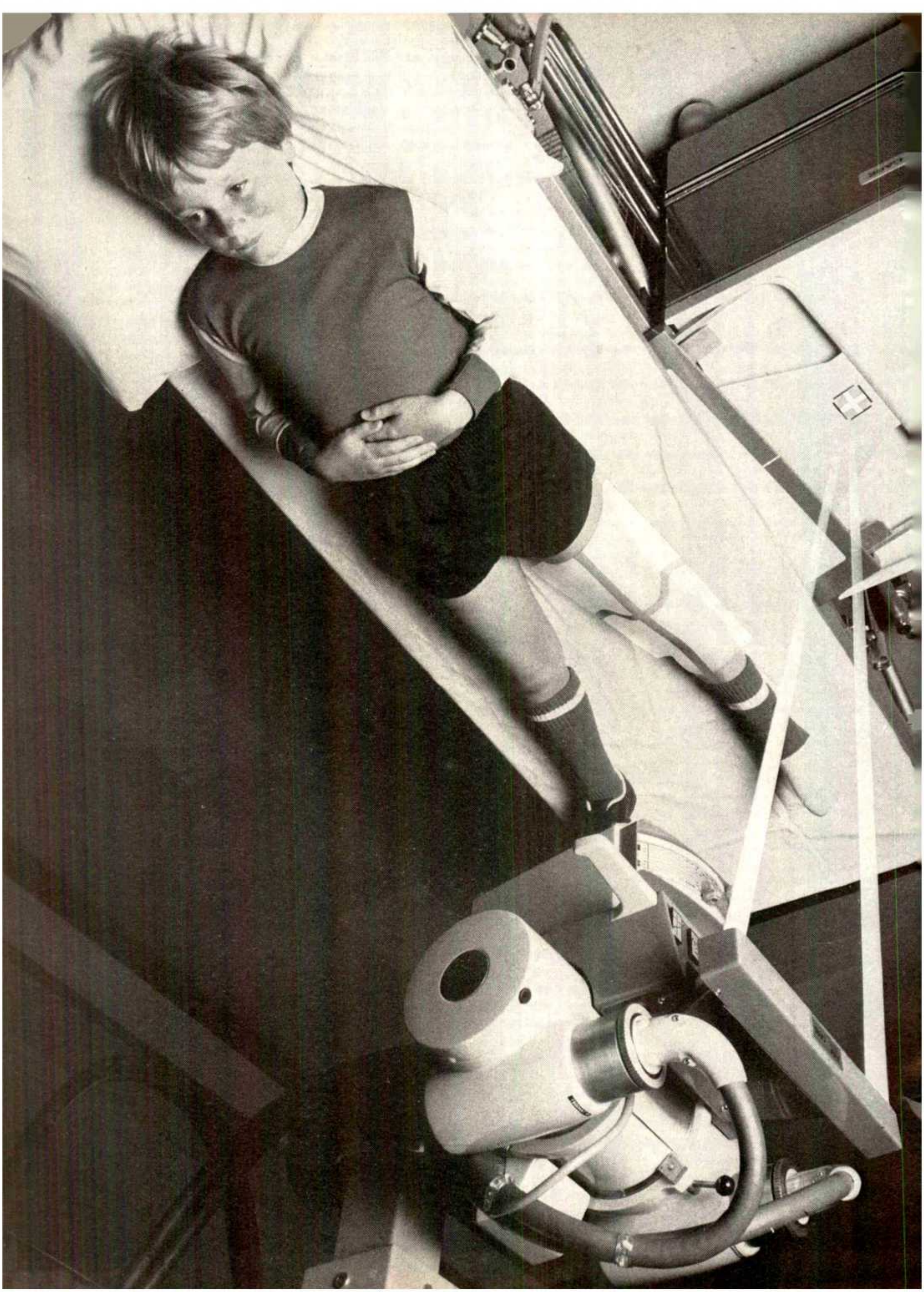

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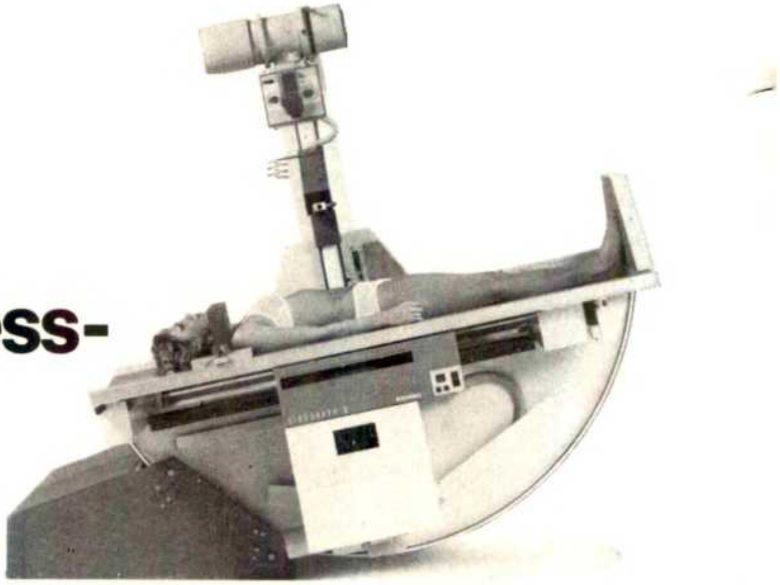

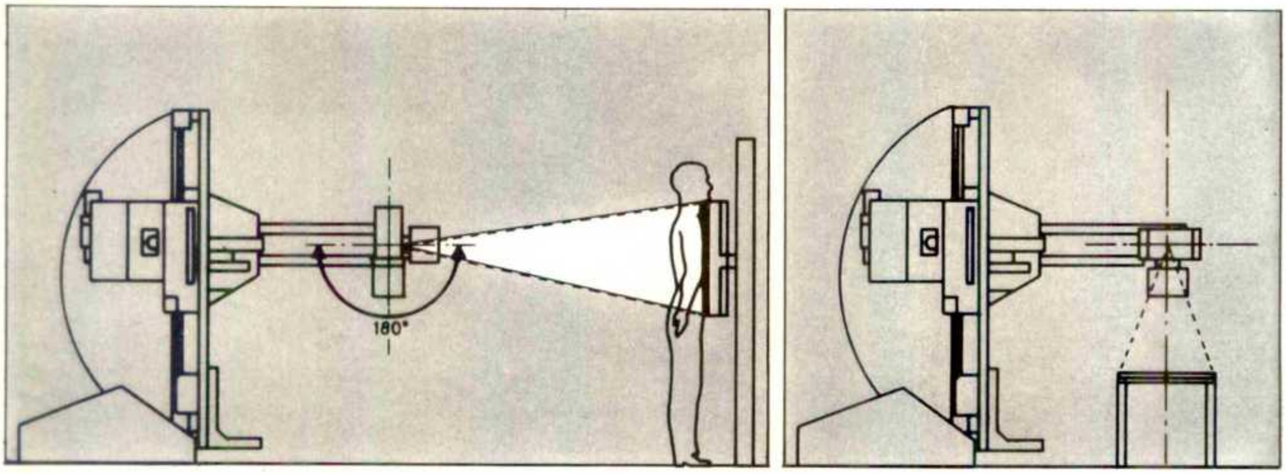

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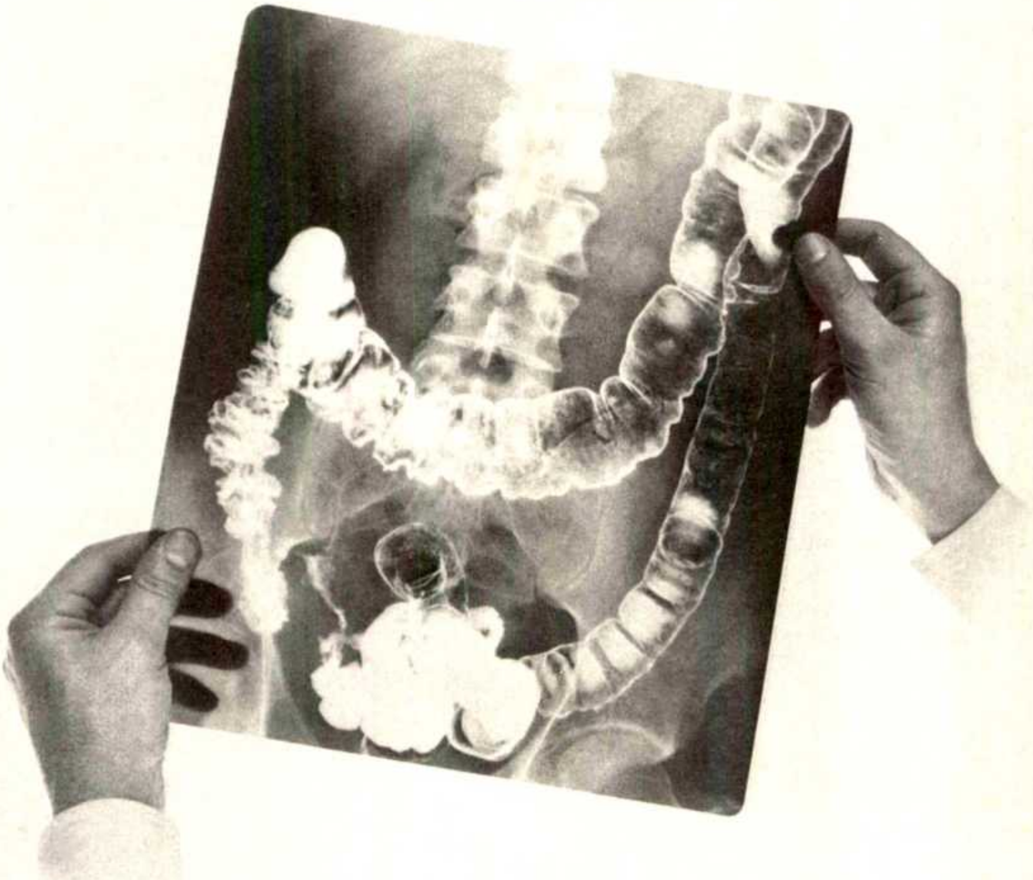

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Thursday 15th June

9.30	Is the Heart Enlarged?	Simon Rees
9.50	Selective Chamber enlargement	Ian Kerr
10.10	Unusual cardiovascular shape	Rosamund Thompson
10.30	Discussion	
11.10	Cardiovascular calcification	Michael Pearson
11.30	Diseases of the Aorta	Maurice Raphael
11.50	Basic echocardiography	Graham Leech
12.10	Discussion	
2.00	Physiology of the pulmonary circulation	Peter Harris
2.20	Radiology of heart failure	Basil Strickland
2.40	Pulmonary angiography and lung scanning	Ian Kerr
3.00	Discussion	
3.20	Film Quiz	

Friday 16th June

9.30	Clinical presentation of Congenital Heart Disease	Jane Somerville
10.00	The chest X-ray in the neonate	Donald Shaw
11.00	The plain film in abnormal situs & venous connexions	Michael Pearson
11.20	Radiological differential diagnosis in the Cyanosed patient	Basil Strickland
11.40	Radiology of continuous murmurs	Simon Rees
12.00	Discussion	
2.00	Computerization of catheter data	Anthony Rickards
2.20	Isotope imaging in cardiology	Duncan Dymond
2.40	CT Scanning of the heart	Michael Thomas
3.00	Left ventricular function in ischaemic heart disease	Thomas Traill
3.20	Radiological assessment of patients for coronary artery surgery	Maurice Raphael
3.40	Discussion	

Application forms and further details from Vice Dean, Cardiothoracic Institute,
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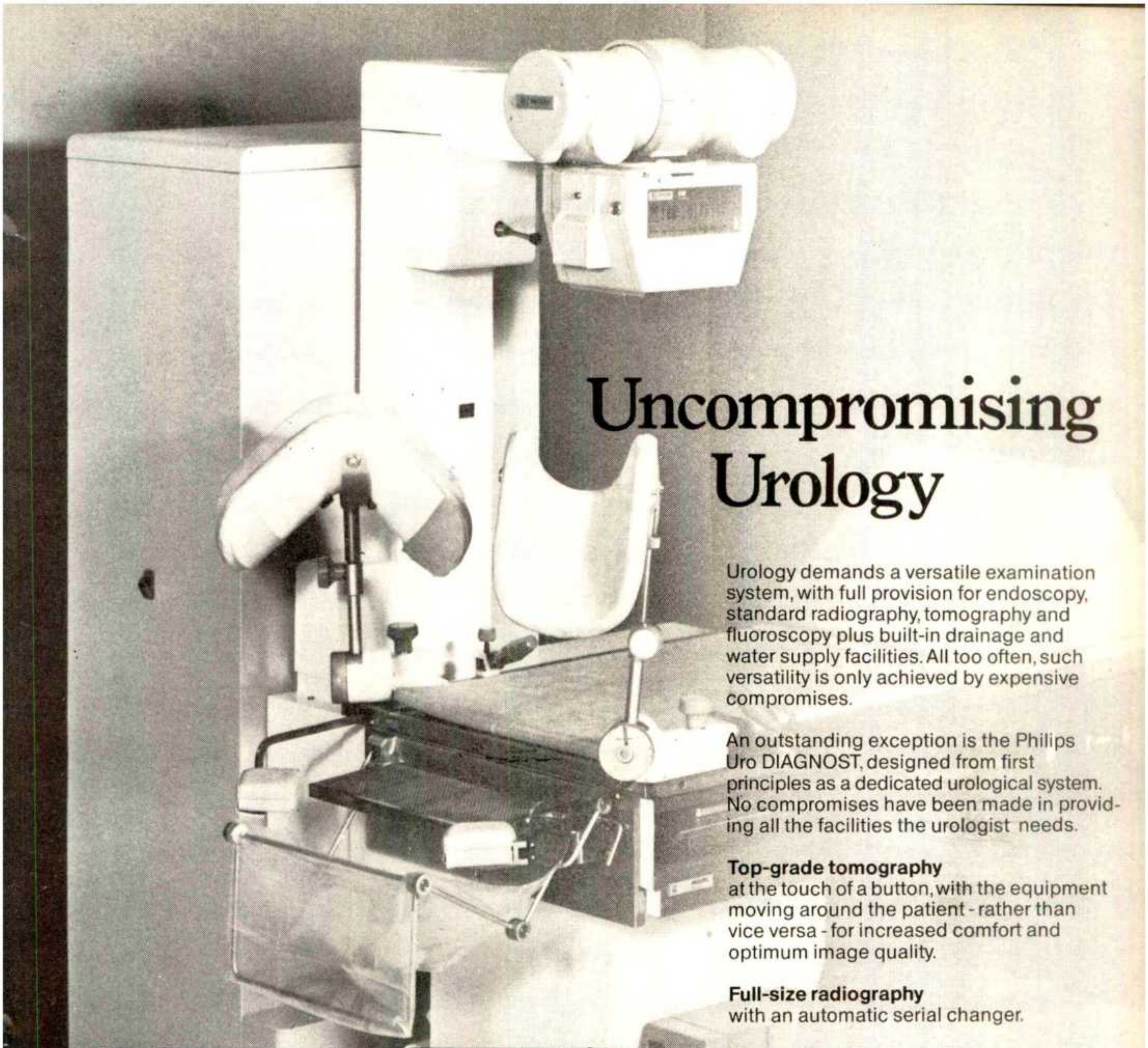

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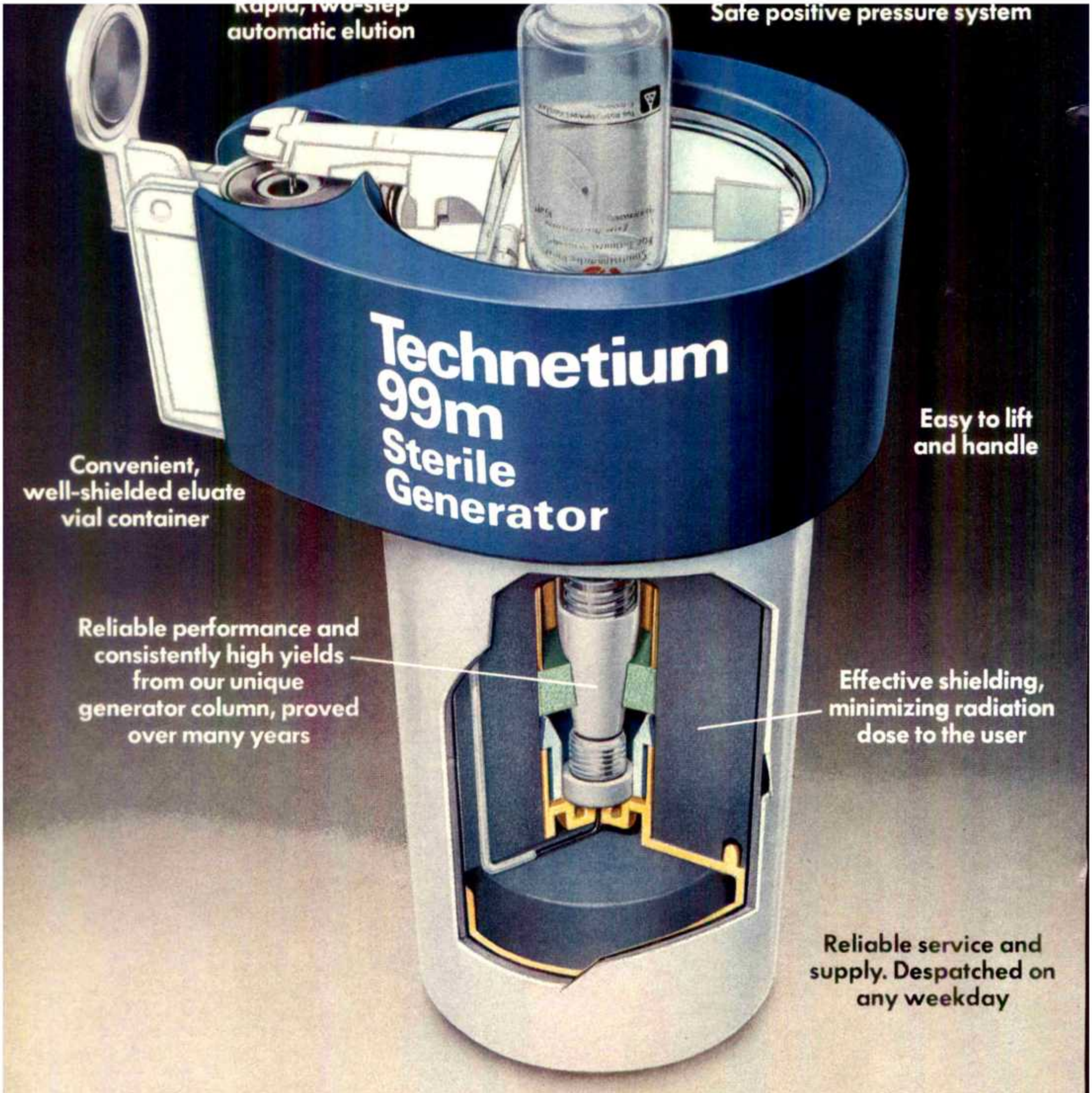

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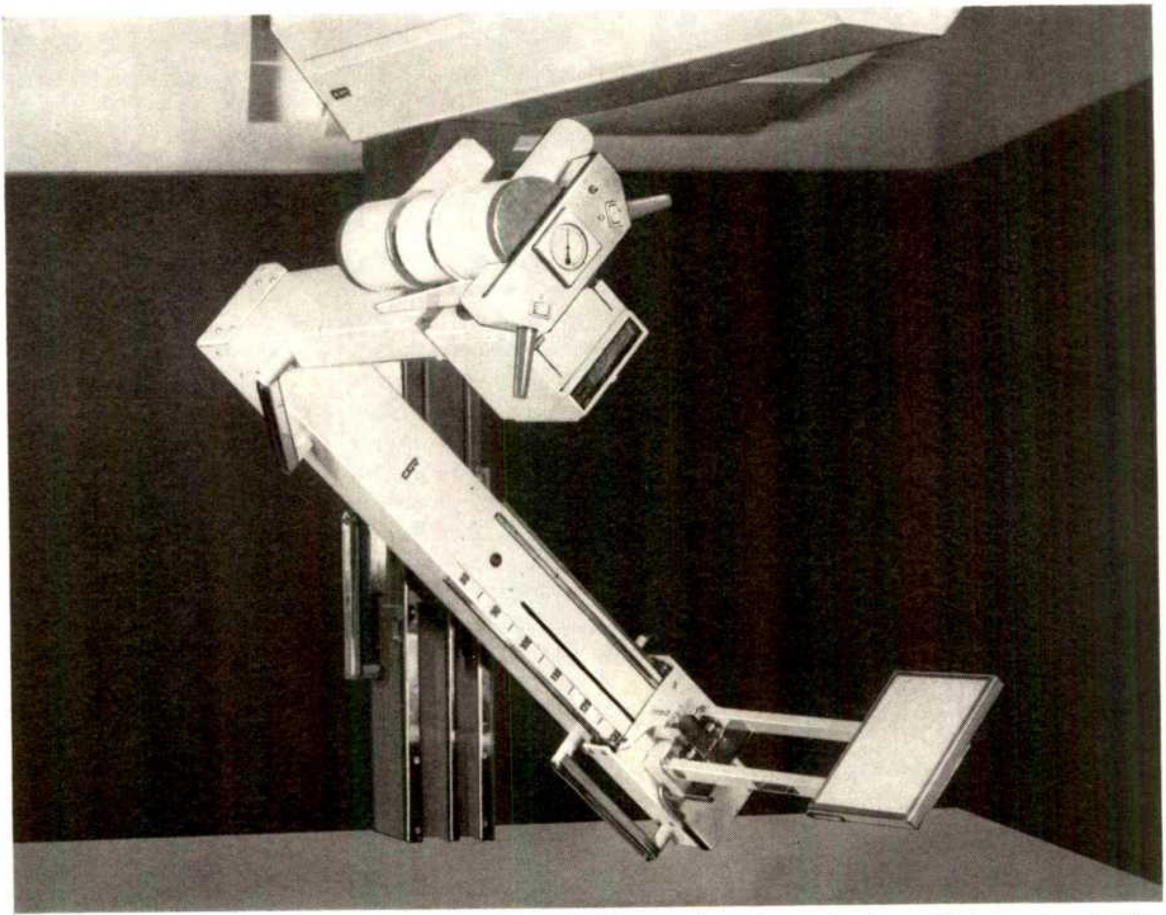

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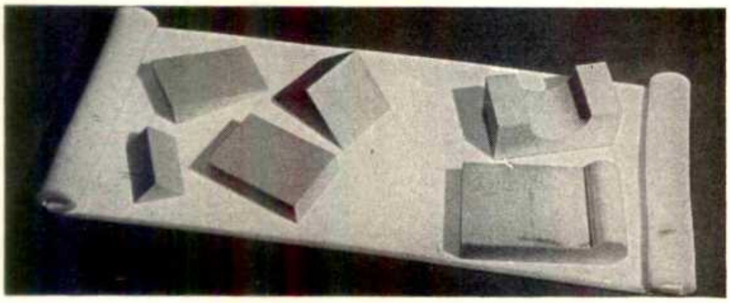

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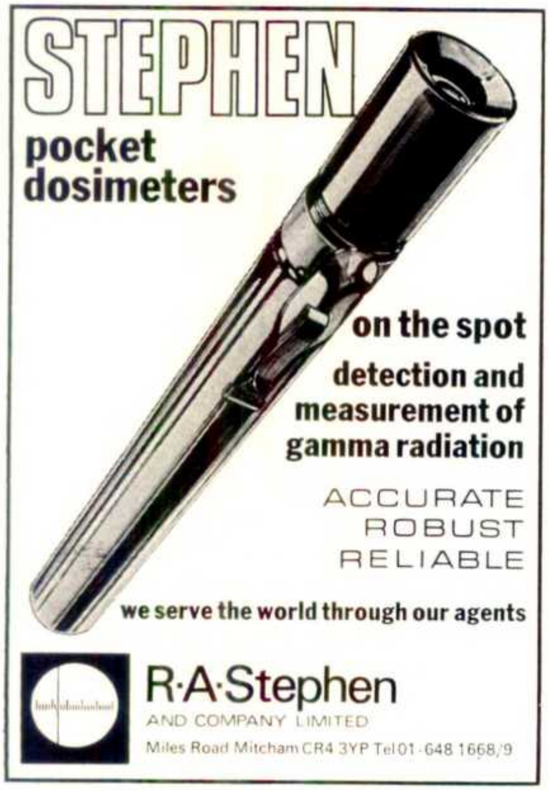

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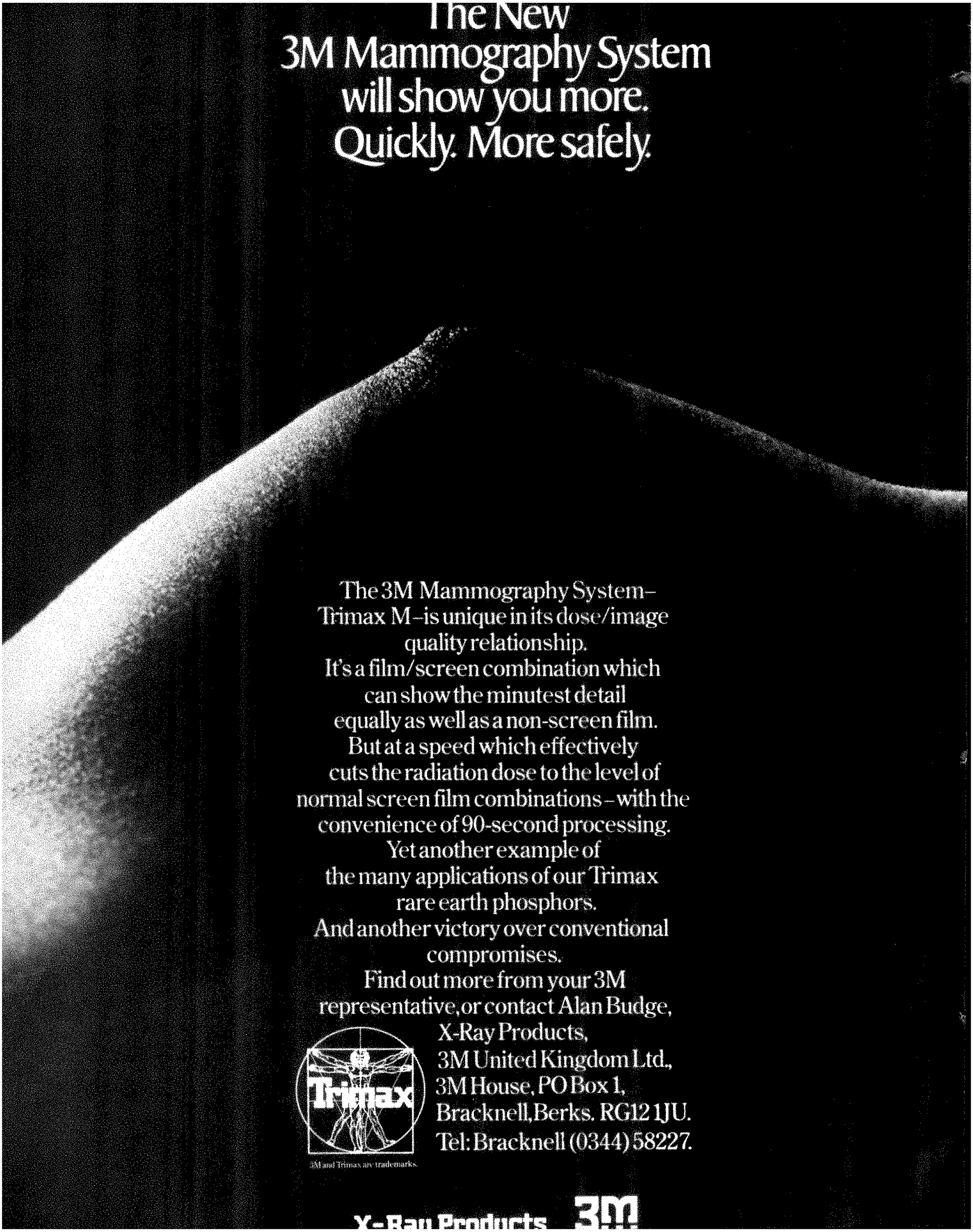

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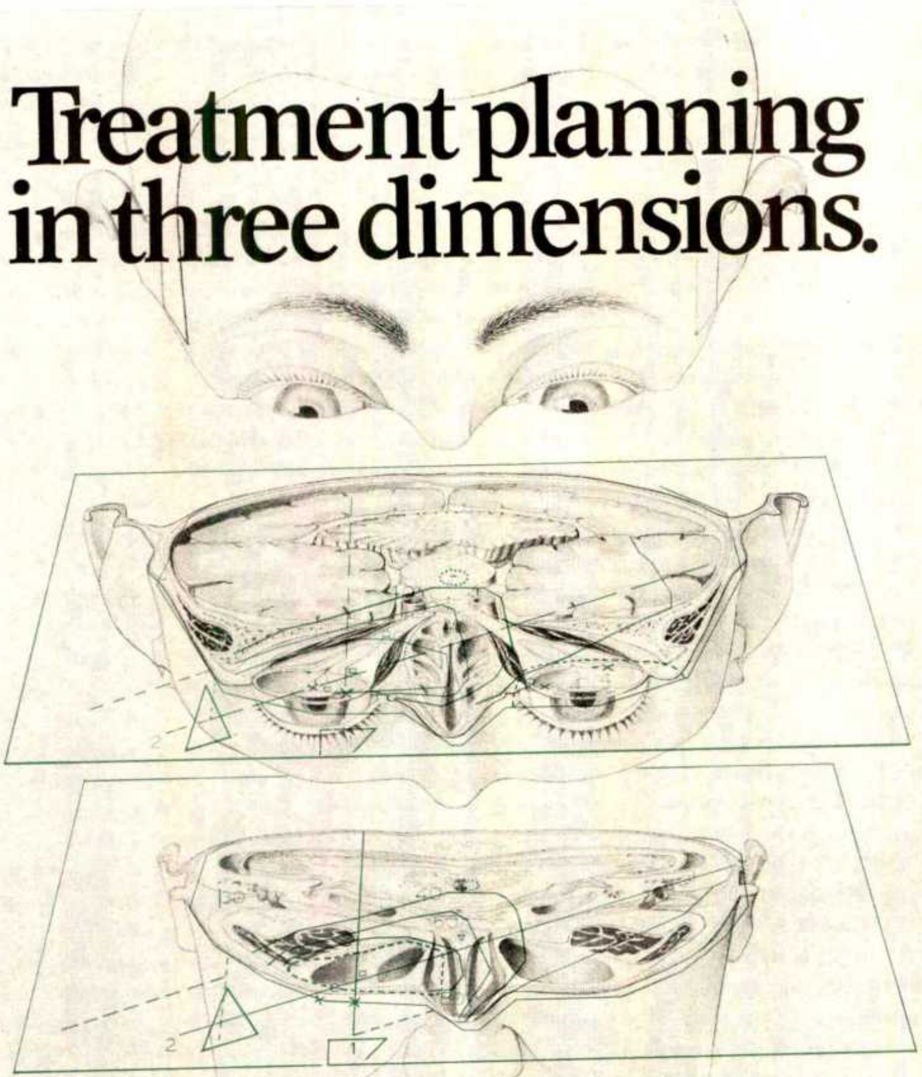

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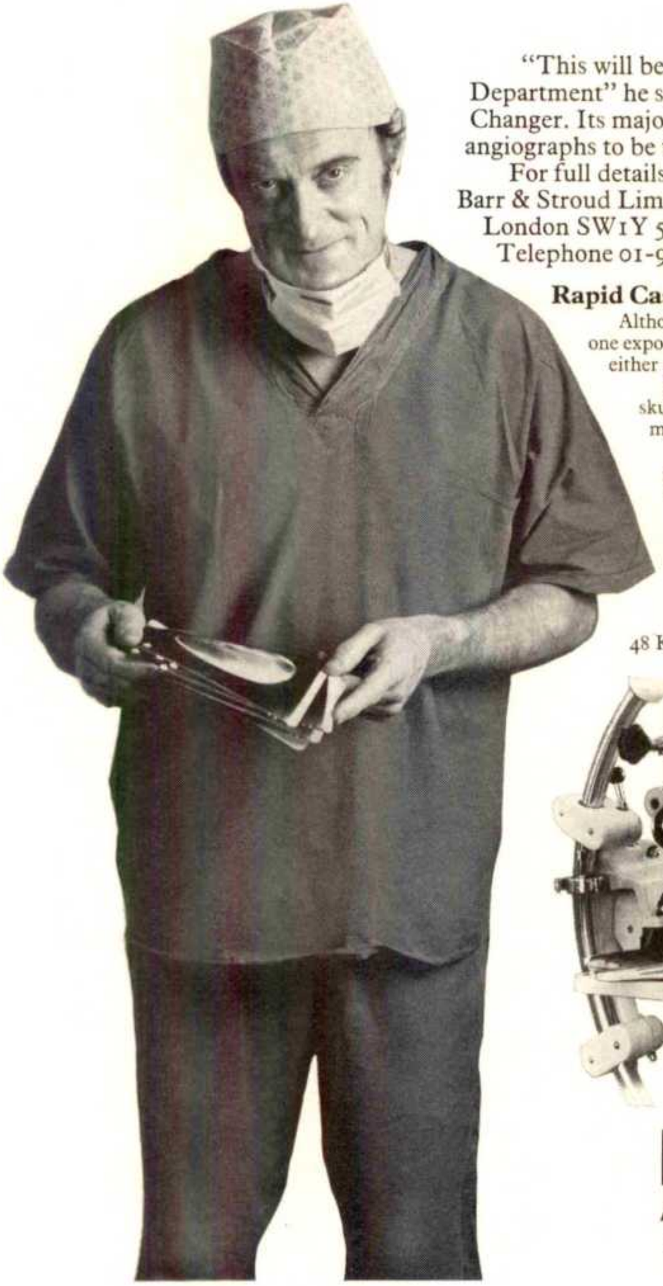

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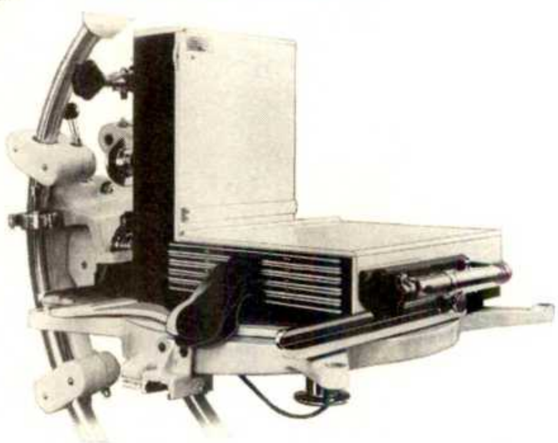

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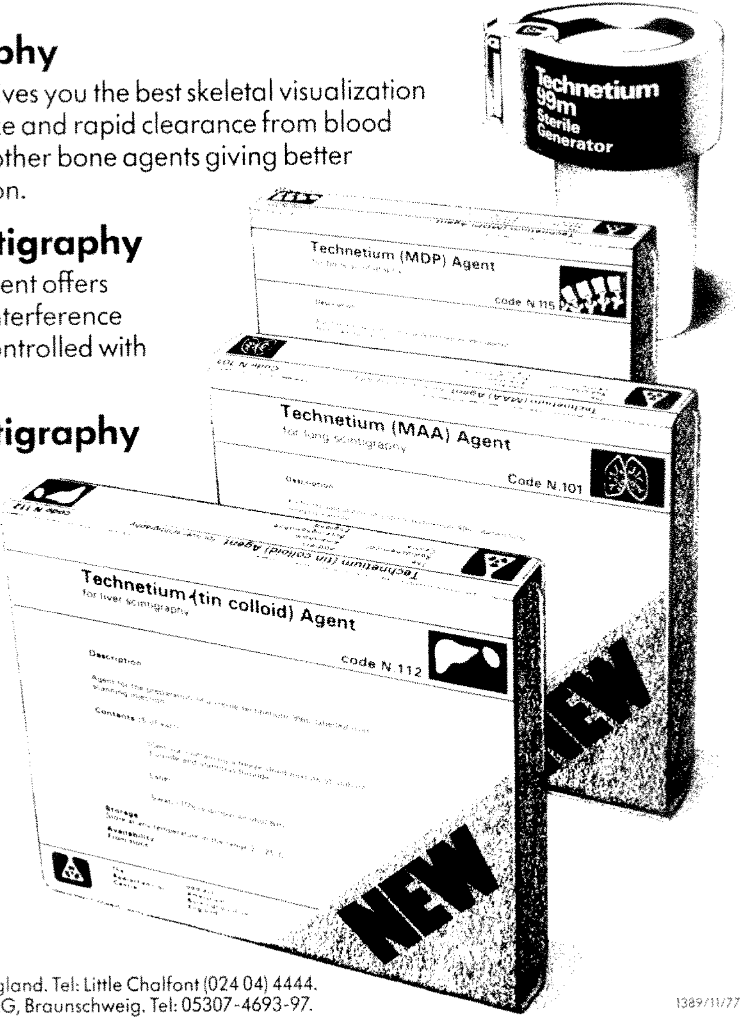

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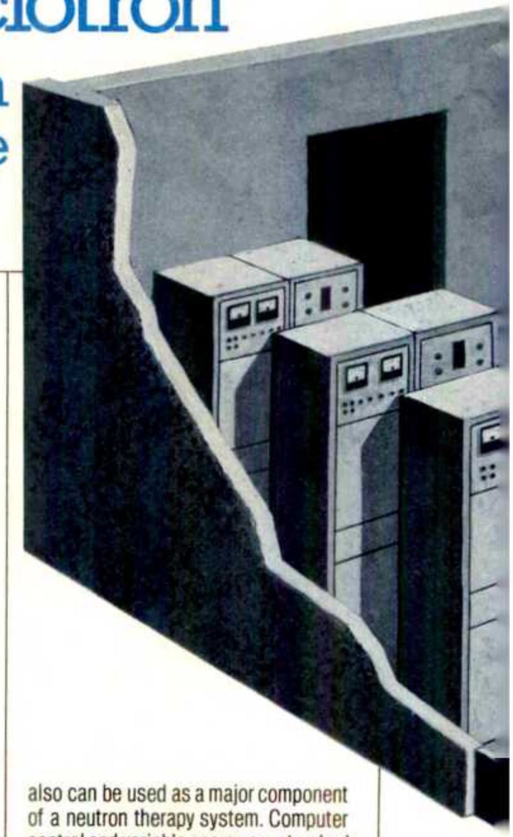

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Another potentially valuable option is complete self-shielding. This can be of particular advantage when it is necessary to make use of existing facilities because of budgetary or other constraints on new construction. As the artist's illustration reveals, this feature permits locating the controls and the Model CP-16 Cyclotron in the same room under "controlled area" conditions.

The standard Clinical Cyclotron™ produces the desired radioisotopes utilizing selected (p,n), (p,xn), and (p, α) reactions shown in the accompanying table. Should a user prefer to employ some or all of the listed (d,n) or (d, α) reactions, this capability is available as an option. Likewise, the ability to vary the energy of the particles accelerated by the Model CP-16 Cyclotron is an optional feature. The energy range applicable to protons is 4-16 MeV; for deuterons, 3-8 MeV.

Drawing on the extensive experience gained in building over 20 cyclotron systems and the advice and counsel of users of these systems, The Cyclotron Corporation also has developed the Model CP-30 Cyclotron. This machine is designed for those users who want to have the ability to produce the full range of medically useful isotopes in the hospital. With the Model CP-30, virtually all of the longer half-life isotopes can be produced in commercial quantities. This cyclotron also can be used as a major component of a neutron therapy system. Computer control and variable energy are standard features of the Model CP-30 Cyclotron. Like the Clinical Cyclotron™ this machine produces protons but the energy range is 8-30 MeV; for optional deuterons, 4-15 MeV.

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Reaction										
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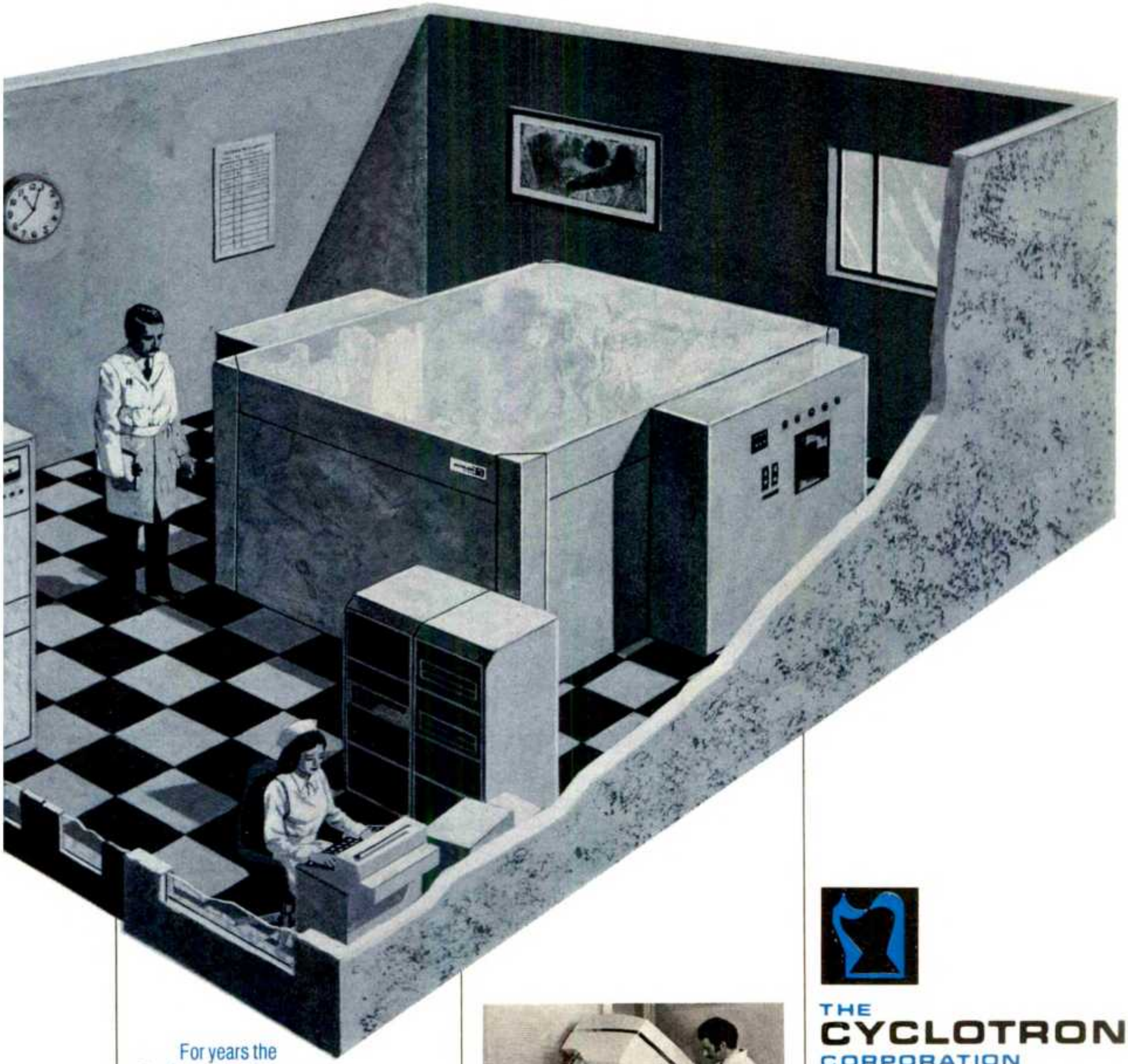
CP-30**	^{14}N(p,α)	^{16}O(p,α) ^{12}C(d,n)	$\boxed{15}$ N(p,n) ^{14}N(d,n) ^{16}O(p,pn)	$\boxed{18}$ O(p,n) ^{20}Ne(d,α)	^{82}Kr(p,2n)	$\boxed{123}$ Te(p,n) $\boxed{124}$ Te(p,2n)	Zn(p,xn) $\boxed{66}$ Zn(d,n) $\boxed{68}$ Zn(p,2n)	Cd(p,xn) $\boxed{111}$ Cd(p,n) $\boxed{112}$ Cd(p,2n)	^{69}Ga(p,2n)	$\boxed{203}$ Tl(p,3n)

NOTE: *Where current use data indicates reaction is possible only with Model CP-30 or significantly higher yields are obtained using CP-30, the reaction is printed in blue.

**Acceleration of deuterons is available as an option.

$\boxed{n}$ Denotes enriched isotope.



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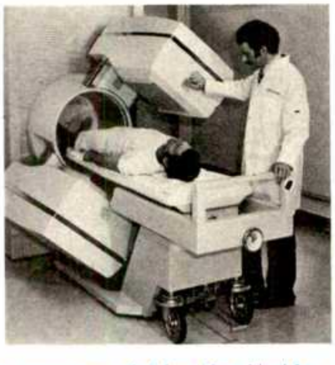

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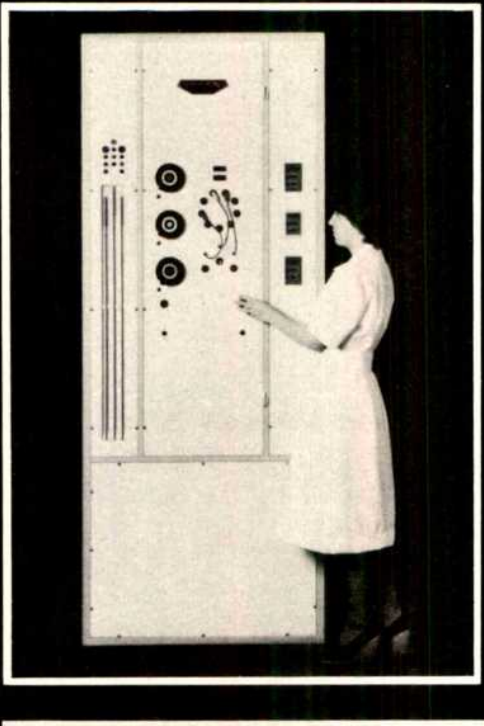

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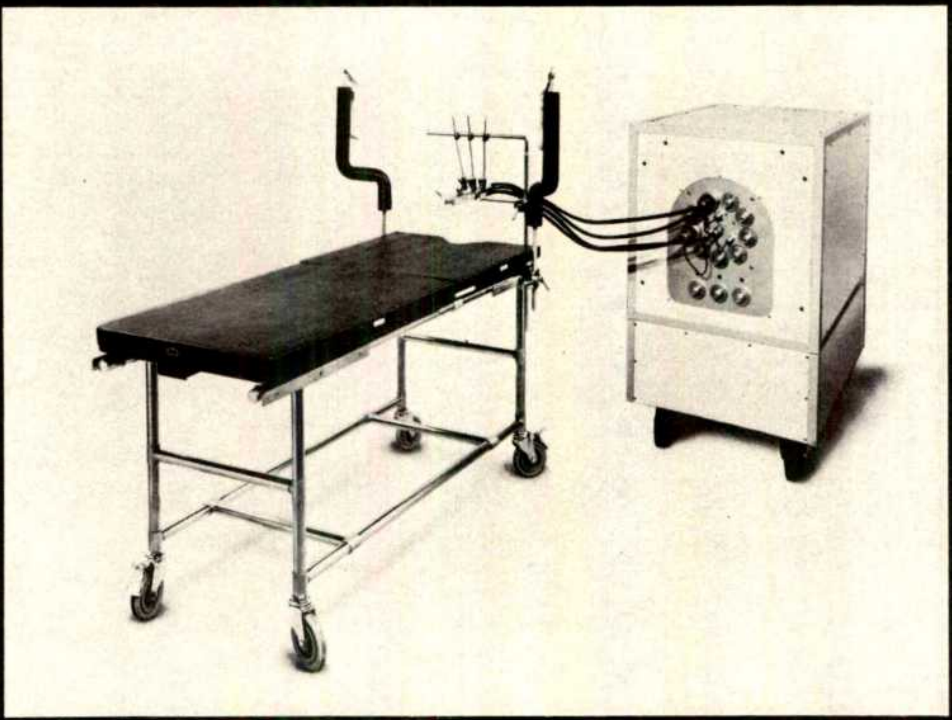

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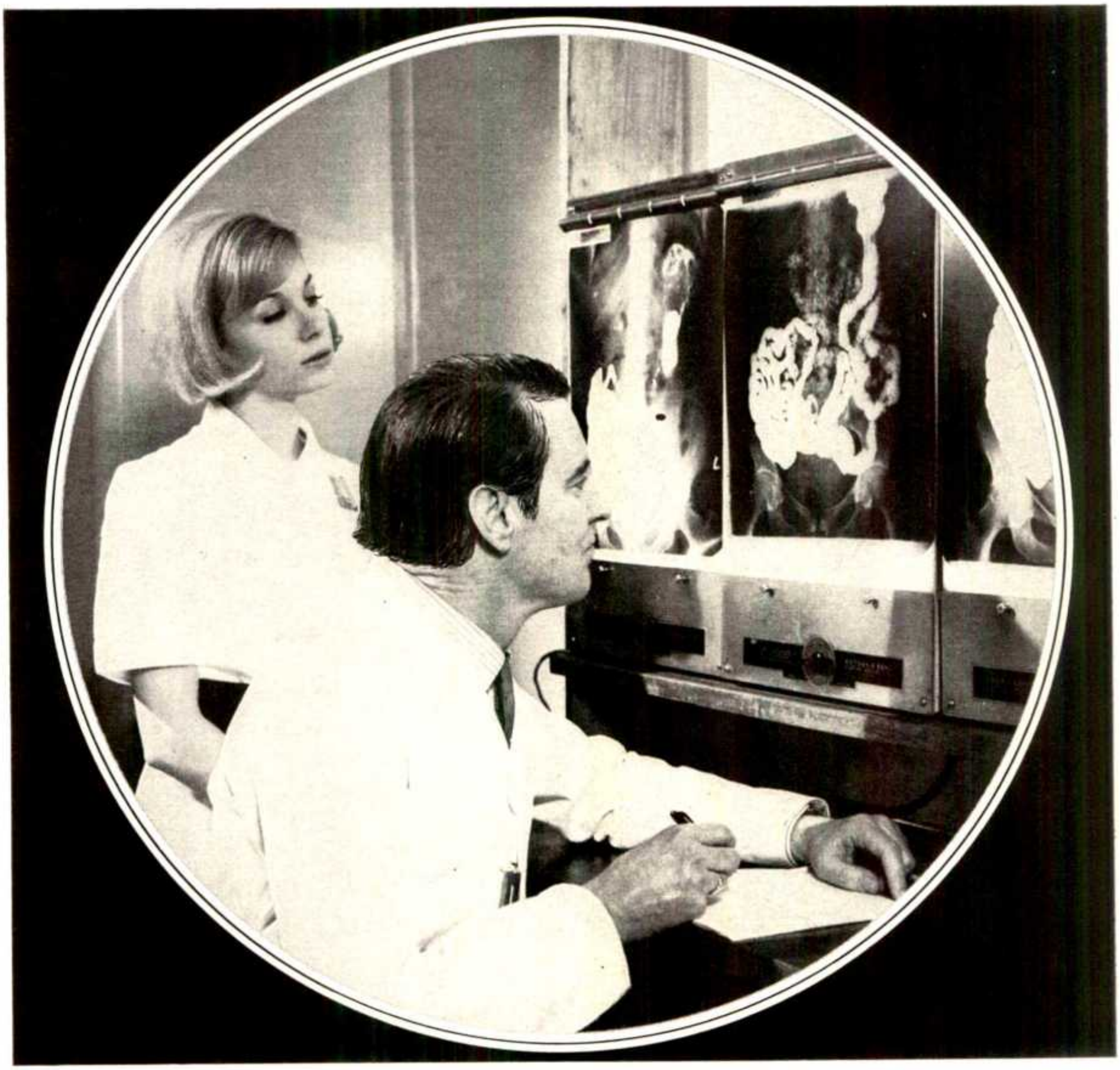

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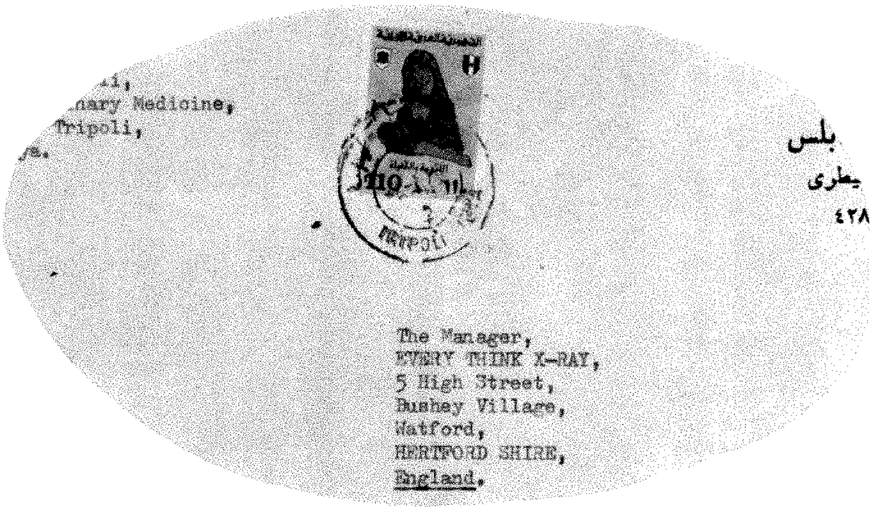

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The British Journal of Radiology

Sixth Interim Progress Report of the British Institute of Radiology fractionation study of 3F/week versus 5F/week in radiotherapy of the laryngo-pharynx*

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ABSTRACT

The results are reported of the multicentre BIR fractionation trial of 3F/week versus 5F/week in radiotherapy of the laryngo-pharynx. 687 patient records have been analysed with respect to survival rates, recurrence-free rates and laryngectomy-free rates. For the group as a whole these analyses show no difference between the two fractionation regimes. Analysis of the sub-group which had early disease confined to the vocal cords does, however, show a better recurrence-free and laryngectomy-free rate for those patients treated with 5F/week, though the survival rate for the two groups remains similar. Acute and late normal tissue reactions are reported for up to six years after treatment.

It appears that treatment with 3F/week can be given safely to patients with advanced disease. The differences between the two treatment groups who had early disease of the vocal cords are discussed, but until more data become available in the future the problems raised cannot be resolved.

In therapeutic radiation the pendulum has swung several times between advocates of single dose treatments and of prolonged treatment schedules spanning several months. Probably most of the possible variations between these extremes, such as multiple fractions per day, protraction, split-course régimes etc., have also been reported at intervals of a generation or so. None of these records, however, satisfy modern criteria for a number of reasons: firstly, at the time of most of the early reports the measurement of the physical dose was inadequate by current standards; secondly, the number of observations from which they drew their conclusions would not be thought sufficient on the basis of our present statistical methods of analysis; thirdly, the biological end-points which were chosen, such as erythema, are too variable in themselves to permit accurate assessment.

In 1963, it appeared appropriate to reappraise the place of fractionation in the light of all the advances that had taken place, having in mind the background of an extensive literature which was of only limited value. The British Institute of Radiology, therefore, set up a Working Party for this purpose which, after due consultation between physicists, radiobiologists, statisticians and radiotherapists, decided to tackle a small aspect of the whole fractionation problem in order to obtain a more valid answer than hitherto. Daily treatment régimes were the rule in the majority of centres throughout the world; it was considered that if it could be shown that treatment on alternate days, namely three fractions per week, gave similar results then this would be a helpful finding. It would spare patients many unnecessary attendances for treatment and in addition it would represent a very material financial saving.

MATERIALS AND METHODS

The laryngo-pharynx was chosen as the most suitable region for the trial as both the tumour and the surrounding normal tissues could be assessed regularly by direct observation so that serial data could be obtained from the same patient over a ten-year follow-up period. It is well known that tumours at primary sites such as the true vocal cord carry a very different prognosis from tumours arising in the piriform fossa; the design of the trial took this into account. Details concerning the malignancy had to be provided which would allow subsequent categorization on the basis of the relevant TNM classification. In order to obtain the maximum number of cases in the shortest time it was decided to accept into the trial any patient who had a histologically verified carcinoma in the laryngo-pharynx region. This simple policy has, in practice, shown itself to be entirely satisfactory. Patients with distant metastases were not elegible.

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*Reprints are available from the BIR, 32 Welbeck Street, London W1M 7PG at 60p per copy or $ equivalent, (remittance with order please).

Patients were entered into the trial from the following centres: Bristol (J. Bullimore, S. Curwen, R. C. Tudway); Coventry (K.Sicher); Exeter (R. C. M. Hadden); Glasgow (J. C. Davidson, K. E. Halnan); Liverpool (M. A. Stewart); London—Charing Cross Hospital (D. O'Connell, N. Howard), London Hospital (W. Shanks), Middlesex Hospital (N. M. Bleehen), Royal Free Hospital (D. Skeggs), St. Thomas Hospital (T. D. Bates, I. F. J. Churchill-Davidson); Newcastle (R. Finney, W. M. Ross); Oxford (K. R. Durrant, F. Ellis, A. H. Laing, C. H. Paine, G. Wiernik); Plymouth (J. Brindle); Reading (J. S. Bunting); Southend (D. L. Phillips); Stoke-on-Trent (R. Lindup, D. Meredith-Brown, E. R. Monypenny).

A large sample of the histological slides from patients entered in the early years of the trial was reviewed (by D. St. J. Brew) and, after much effort to obtain a complete set of good slides, no serious discrepancies were found in the histological gradings.

At each centre, when the decision had been taken that the patient was eligible for the trial, a sealed envelope was opened which specified either three or five fractions per week. The same overall time was used for both schedules in a given centre. Thus each centre contributed approximately equal numbers to both arms of the trial (Table I).

A reduction in total radiation dose was employed for treatments with 3F/week compared with 5F/week. This reduction was 11 to 13% for overall treatment times of six to three weeks respectively, as listed in Table III of the Second Progress Report (1968). The radiation was delivered by cobalt 60 machines or linear accelerators, with wedges where appropriate.

TABLE I
Numbers of patients analysed*

Code no. of centre	3F/wk	5F/wk
11	61	65
12	10	14
14	71	67
15	8	15
16	9	8
17	5	7
18	6	3
19	29	23
20	7	11
21	54	56
22	6	8
23	2	5
24	24	37
25	13	14
26	8	9
27	16	12
29	2	2
Totals	331	356

*After withdrawing 9 (see text)

The BIR Working Party on the effects of dose fractionation in radiotherapy has reported on six previous occasions (1963; 1964; 1968; 1970; 1971 and 1972) but as six years have elapsed since the 5th Interim Progress Report (1972) it appears appropriate to provide an up-to-date account. A further 310 new patients have been entered into the trial which has now been closed, as planned. A new trial comparing a short with a long overall time for a course of radical irradiation to the laryngo-pharynx areas has been launched. Sufficient time has now passed to allow us to evaluate data on some of the late radiation reactions, although the final analysis is still several years ahead. Follow-up of the patients in this trial will of course continue.

The total number of patients admitted up to the end of the trial (December, 1975) was 732 from 17 centres of radiotherapy and oncology in the U.K. Three centres contributed over 100 patients each and two others over 50. The records of 696 patients who have been followed up for more than 12 weeks have been checked and entered into the computer by I. F. Lansley and P. Francis: 338 at 3F/week and 358 at 5F/week. Twenty-two of the remaining 36 are being checked for missing data, most of which will be obtained. Nine patients have been excluded from the analysis because they were not followed up (Table I).

The reasons for seven of these exclusions were stated in the Fifth Interim Progress Report (1972); Nos. 11012, 12017, 14039, 15015, 20002, 20004 and 24021. Two others have been withdrawn since then: 21073, lung metastases found soon after start of treatment; 24047, given both 3F and 5F per week during treatment. Of these nine in all, six drew 3F/week and three 5F/week. Thus data for 687 patients have been analysed with follow-up periods of at least six months.

As in the previous interim analyses of this trial, observed survival rates and an analysis of early reactions up to 12 weeks are reported. In addition we now present for the first time local recurrence-free rates, laryngectomy-free rates and an analysis of 12 different types of late normal-tissue reaction recorded up to six years after treatment.

The data are presented in seven tables and four figures. Not all the normal-tissue reactions are presented graphically; some were recorded with negligible frequency and these are presented only in the tables. The list of figures and tables provides an index of the results.

Table I List of centres with number of patients followed up for more than 12 weeks and available for analysis in January 1977.

Table II Significance tests on the curves in Figs. 1, 2 and 3.

Table III Reactions in normal tissues up to 12 weeks after start of treatment (marked mucous membrane reaction, oedema, dysphagia).

Table IV Late reactions in mucous membranes (telangiectasia, atrophy, oedema).

Table V Late reaction in skin (telangiectasia, subcutaneous fibrosis, atrophy, dyspigmentation).

Table VI Other late reactions (pain, dysphagia, probable myelitis and perichondritis).

Table VII Necrosis (in skin, mucous membranes or cartilage).

Figure 1 Observed survival rates (all sites, tumours confined to mobile vocal cords, and sites other than mobile vocal cords). The rates are calculated by the life table method and uncorrected for age. The numbers along the abscissae are the numbers of patients followed up to at least that time.

Figure 2 Local recurrence-free rates (sites as in Fig. 1).

Figure 3 Laryngectomy-free rates (sites as in Figs. 1 and 2).

Figure 4 Graph of certain late reactions versus time.

RESULTS

Observed survival rates

There are no significant differences, between 3F and 5F per week, in observed survival rates for any of the site classifications (Fig. 1). There is, however, a highly significant difference in survival rate between patients with lesions classified as "cords mobile" (confined to vocal cords) and those with a lesion in a different site ($X^2=112$).* This difference confirms that the subdivision is an important one to make when analysing the results. Recurrence-free rates and laryngectomy-free rates are also much higher for "cords mobile" cases than for other sites: $X^2=64$ and 23 respectively for the nine-year period. (These differences are not shown in a graph).

Recurrence-free rates

Recurrence-free rates for "all sites" are not significantly different for the two fractionation régimes (Fig. 2a), nor are recurrence-free rates for "sites other than cords mobile" (Fig. 2c). For "cords mobile", however, the 5F/week patients have a higher recurrence-free rate than those treated at 3F/week (Fig. 2b) and the difference, although small, is significant ($X^2=4.91$, $P=0.026$). This subgroup represents about 40% of all the patients analysed.

Laryngectomy-free rates

Laryngectomy-free rates show the same trend. There are no significant differences for either "all sites" or for "sites other than mobile vocal cords" Figs. 3a and c). For "cords mobile", however, the laryngectomy-free rate is higher in the 5F/week than in the 3F/week patients ($X^2=4.97$, $P=0.024$) as shown in Fig.3b.

This result is consistent with a separate, more detailed check that was carried out, by writing to the radiotherapists concerned, to establish the reason for each laryngectomy. Among the total of 142 laryngectomies which were carried out, the histological report on the specimen recorded no evidence of malignancy in only seven cases. Very few cases of necrosis occurred (Table VII) and in all except one the presence of malignancy was confirmed by the histological report. Laryngectomy was, therefore, carried out almost exclusively for local recurrence and not for necrosis; the laryngectomy rates and the recurrence rates, which can be derived from the data shown in Figs. 2 and 3, can be seen to be in close agreement. In the "cords mobile" category there were 11 versus 25 recurrences and 13 versus 28 laryngectomies for the 5F/week versus 3F/week treatments respectively.

The same trend was seen in each of the three centres contributing the most patients when these were analysed separately, although in no centre alone was the difference significant. An analysis was performed, for four large centres, of the doses actually given and of the normal tissue reactions recorded in the laryngectomy versus the laryngectomy-free cases, but no trends were found. It cannot, therefore, be shown that lower doses were given to those cases which were subsequently submitted to laryngectomy because of local recurrence. No trends were found for the centres which used overall times of 25 to 30 days as compared with 39 to 45 days.

When recurrence-free rates are considered, 5F/week does seem to improve the results in patients with mobile cords. Considered alone by the logrank test the difference is significant ($0.05>P>0.025$); but when an overall test is done on the data the P-value is between 0.1 and 0.05 for all patients (see

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*X^2 is the statistic calculated by the Logrank test as described by Peto *et al.* (1977). When two groups are being compared the corresponding values of P are as follows.
$X^2=2.71$ 3.84 5.02 6.63 7.88 10.83
$P=0.01$ 0.05 0.025 0.01 0.005 0.001

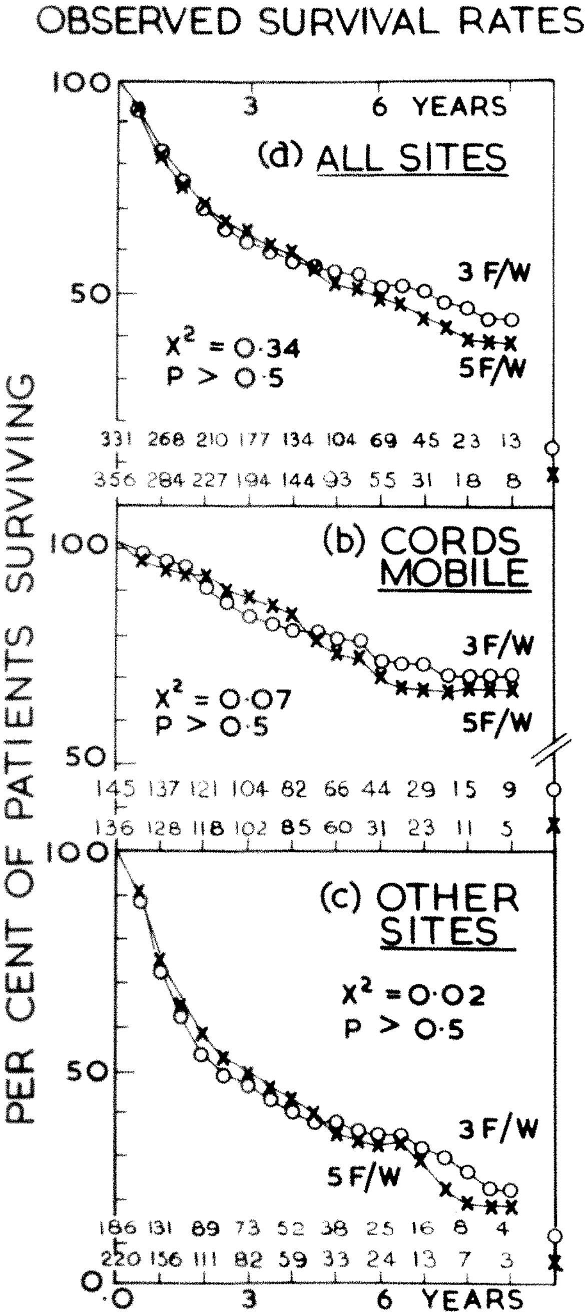

Fig. 1.

Observed survival rates of patients versus time after treatment. The numbers of patients surviving at each anniversary are shown along the bottom. Upper row: 0:3F/week. Lower row: X:5F/week. The values of X^2 are for the logrank test as defined by Peto *et al.* (1977). *P* greater than 0.5 means not significantly different. No correction for age of the patients or mortality of patients without cancer is made. "Cords mobile" means tumour confined to the vocal cords

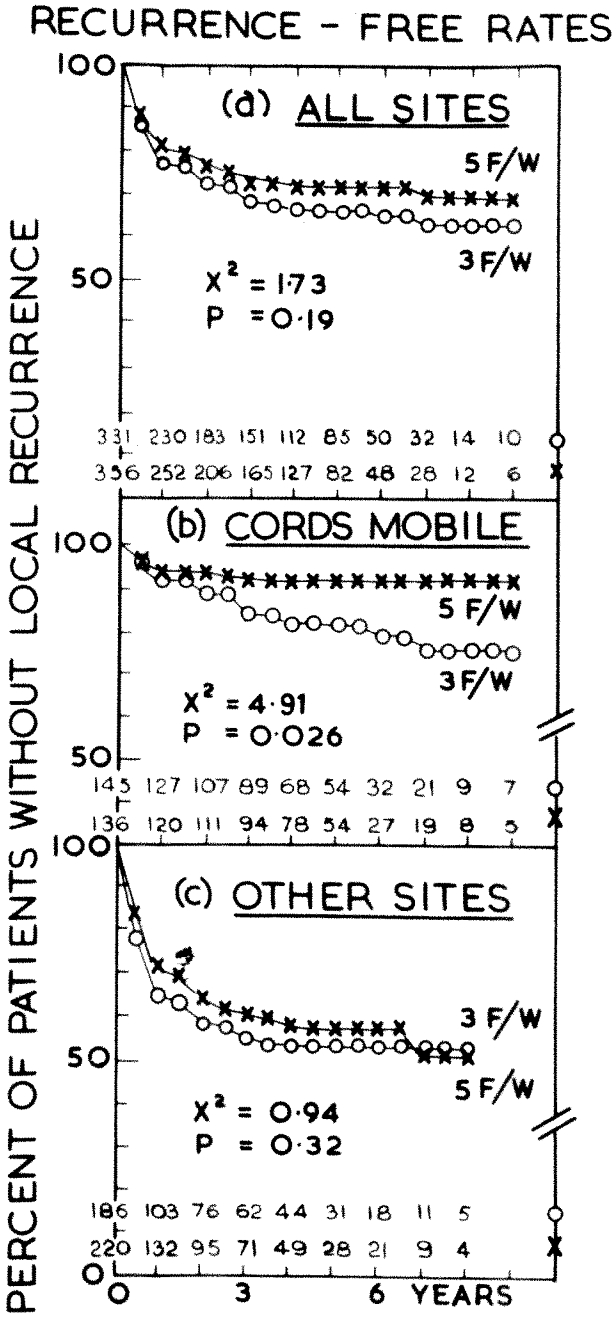

Fig. 2.

As Fig. 1 for the proportion of patients who experienced no local recurrence. *P* less than 0.05 is probably significant (but see Table II).

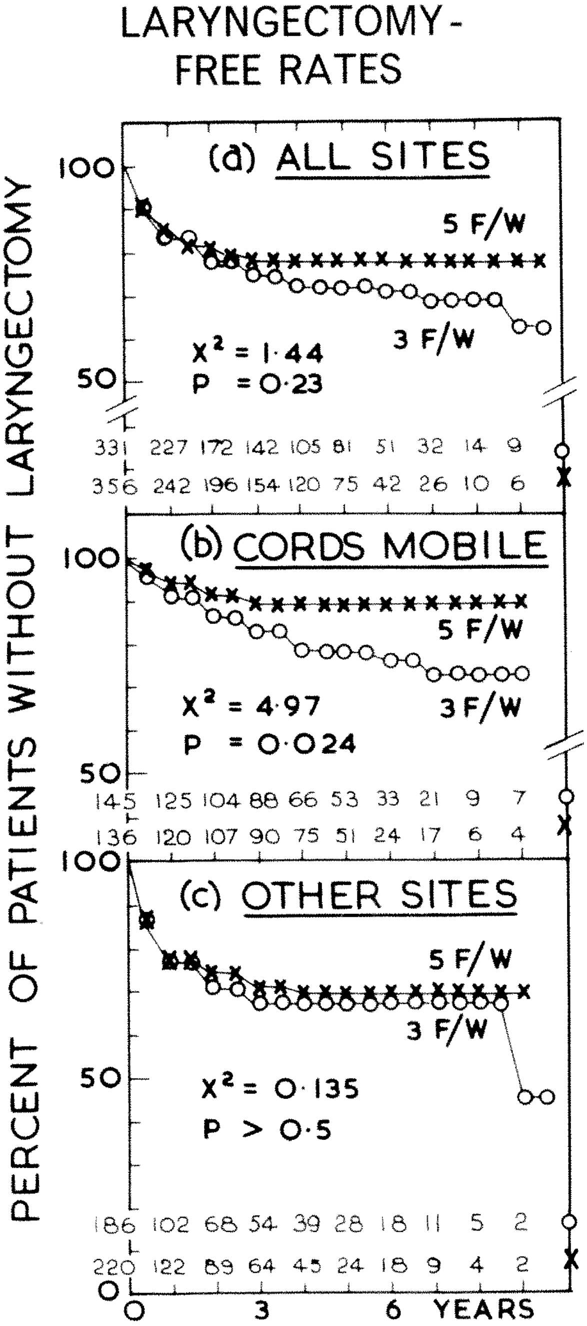

Fig. 3.

As Figs. 1 and 2 for the proportion of patients who have not had a laryngectomy.

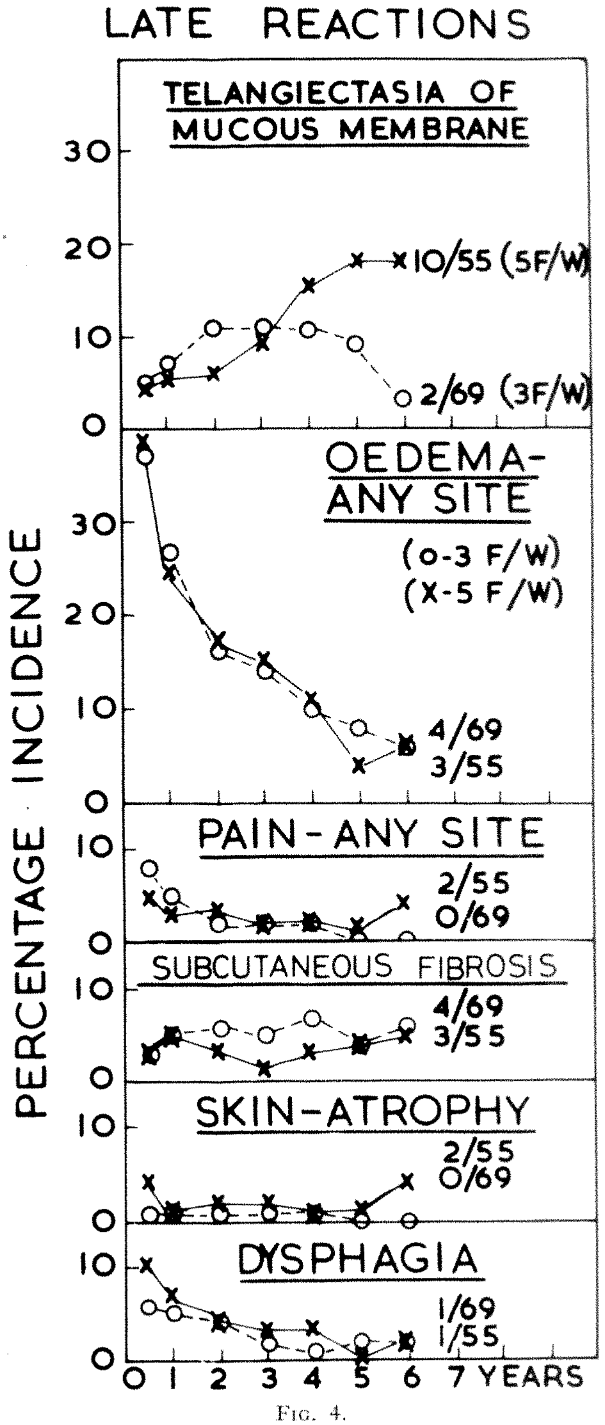

Fig. 4.

Percentage incidence of normal tissue reactions recorded in each annual interval (except the first two six-month periods). Crosses—5F/week. Circles—3F/week.

Table II). The latter values are probably more reliable and suggests that the improvement is only very small.

A similar result is obtained for laryngectomy-free rates except that in this case the *P*-value for the overall test is greater ($0.2 > P > 0.1$); this difference is not significant.

Although the differences are small and the statistical significance is not very great, the results from the doses used in this trial suggest that in the sub-group with the best prognosis, "cords mobile", daily fractionation may be followed by fewer local recurrences; the survival of the patients, however, was not affected because those with recurrence could be cured by subsequent laryngectomy. The possible causes for this result are dealt with in the discussion.

Normal tissue reactions

The normal tissue reactions show fewer differences. The three early reactions recorded in Table III are greater for 5F/week than 3F/week, but none are significantly different. Although it is highly probable that the last column means "reaction absent", we have presented the data in Table III as they were recorded.

The late reactions seen in the mucous membrane show that although telangiectasia appears to occur more frequently in 3F/week than 5F/week cases before three years the reverse is true after that time (Table IV) but none of the differences are significant (Fig. 4). In the skin, late subcutaneous fibrosis and atrophy are also not significantly different for 3F/week or 5F/week (Table V). Other late reactions (Table VI) show no significant differences.

The numbers of patients with necrosis are small and are similar in the two groups (Table VII). The centres concerned have reviewed the original hospital records of the patients in whom necrosis was reported, in order to determine whether these patients had persisting or recurring tumour which might have been mistaken for radiation necrosis. Only those patients who were confirmed as being free of viable tumour tissue, so that necrosis was attributable to excessive radiation dose to the normal tissue, are listed in Table VII as having "confirmed necrosis". It was found in one centre, for example, that four out of the six patients who had been reported as having necrotic ulceration at six months in fact had recurrences which were only identified subsequently.

An attempt was made to determine a dose-response relationship by dividing the patients in Centre 11 into three groups according to the dose which they received. The modal doses actually given (taken from the 12-week follow-up form) were arranged in sequence with the object of comparing survival rates for the one-third receiving the lowest

TABLE II

SIGNIFICANCE TESTS ON WHOLE CURVES (B) AND (C) IN FIGS. 1, 2 AND 3; THEN COMBINED

Site	5F/wk		3F/wk		X^2	P (1 deg. of freedom)
	Expected	Observed	Expected	Observed		
Deaths						
Cords mobile	28.960	30	31.039	30	0.072	0.4
Other	127.112	126	108.887	110	0.021	>0.5
Recurrences						
Cords mobile	17.649	11	18.351	25	4.914	0.026
Other	84.969	79	69.030	75	0.936	0.33
Combined	102.618	90	87.381	100	3.39	0.065
Laryngectomies						
Cords mobile	20.133	13	20.867	28	4.965	0.024
Other	54.826	53	45.173	47	0.135	>0.50
Combined	74.959	66	66.040	75	2.28	0.13

The values of X^2 for "cords mobile" and "other" are taken from Figs. 1, 2 and 3, panels (b) and (c) respectively.

To make an overall comparison between the two treatment régimes taking into account the very different prognosis of "cords mobile" and "other" patients, the results for recurrences and laryngectomies are then combined in this table. The resulting comparison is thus more refined than that shown in panels (a) of Figs. 2 and 3 and leads to higher values of X^2 and consequently lower values of *P*, but the combined differences are still not significant and there is no change in the conclusions. No such combined group is presented for deaths because the difference is obviously not significant.

TABLE III

Reactons in normal tissues up to 12 weeks after start of treatment

	Present		Absent		Presence or absence not recorded	
All centres	3F/wk	5F/wk	3F/wk	5F/wk	3F/wk	5F/wk
Patients analysed	331	356	331	356	331	356
Marked mucous membrane reaction (fibrinous reaction or ulceration)						
At any time	212	254	50	55	69	47
Longer than 4 weeks	48	70	213	215	70	71
Oedema						
At any time	127	149	105	118	99	89
Longer than 4 weeks	47	66	215	237	69	53
Dysphagia						
At any time	205	226	65	69	61	61
Longer than 4 weeks	73	95	194	192	64	69

Assuming that "not recorded" means "absent" and analysing data for longer than 4 weeks, we obtain:

	3F/wk	5F/wk	X^2	P
Marked mucous membrane reaction	48 (15%)	70 (20%)	3.06	0.075 NS
Oedema	47 (14%)	66 (18%)	2.02	0.15 NS
Dysphagia	73 (22%)	95 (27%)	1.77	0.18 NS

TABLE IV

Late reactions in mucous membranes

	Present		Absent		Not recorded	
All centres (years)	3F/wk	5F/wk	3F/wk	5F/wk	3F/wk	5F/wk
Patients analysed	299	326	299	326	299	326
Telangiectasia						
½	16	11	260	291	23	24
1	18	15	222	239	24	22
2	22	13	159	188	25	24
3	20	17	134	141	21	25
4	15	22	99	106	20	17
5	9	17	84	64	11	12
6	2	10	55	35	12	10
Atrophy ½	4	2	264	289	31	35
1	4	3	233	242	27	31
2	4	6	178	194	24	25
3	3	5	151	152	21	26
4	3	5	112	122	19	18
5	5	4	86	76	13	13
6	1	3	56	42	12	10
Oedema (any site)*						
½	110	129	173	182	16	15
1	71	68	177	197	16	11
2	33	37	150	174	23	14
3	25	19	134	148	16	16
4	13	11	108	127	13	7
5	8	4	89	84	7	5
6	4	3	57	47	8	5

*80 to 95% of oedema was in the treated volume.

TABLE V

Late reactions in skin

All centres (years)	Present		Absent		Not recorded	
	3F/wk	5F/wk	3F/wk	5F/wk	3F/wk	5F/wk
Patients analysed	299	326	299	326	299	326
Telangiectasia						
½	2	3	281	306	16	17
1	2	2	251	259	11	15
2	2	1	189	210	15	14
3	3	3	161	167	11	13
4	2	0	120	133	12	12
5	1	0	100	87	3	6
6	0	1	64	50	5	4
Subcutaneous fibrosis						
½	3	10	306	266	23	31
1	2	13	259	234	17	26
2	1	12	210	178	16	16
3	3	8	167	154	13	16
4	0	9	133	113	12	13
5	0	4	87	97	3	8
6	1	4	50	59	6	5
Atrophy ½	1	4	274	290	24	32
1	1	2	246	248	17	26
2	1	4	188	203	17	18
3	1	4	160	164	14	15
4	1	2	121	130	12	13
5	0	1	101	84	3	8
6	0	2	64	48	5	5
Dyspigmentation						
½	16	24	260	270	23	32
1	6	15	241	236	17	25
2	9	9	180	199	17	17
3	7	5	155	163	13	15
4	4	2	118	130	12	13
5	4	1	97	84	3	8
6	0	2	63	48	6	5

doses with those in the third receiving the highest doses.

	3F/week (61 pts)	*5F/week (66 pts)*
Low doses	4947–5100 rad (10 pts)	5400–5984 rad (6 pts)
Medium doses	5130–5250 rad (48 pts)	6000 rad (56 pts)
High doses	5300–5370 rad (3 pts)	6012–6120 rad (4 pts)

There was not a sufficient spread in the doses to justify this attempt and no significant difference in average survival time was seen between the low and high dose groups: it is of course, satisfactory that the distribution of modal doses delivered was narrow.

Discussion

The normal tissue reactions show only small differences none of which are significant. The suggestion has to be considered, however, whether the doses used for the 3F/week schedules had a lower biological effectiveness than those used for 5F/week, but there is no significant evidence for this, even for the early reactions in Table III. Changes in normal tissue reactions would, of course, be harder to detect than changes in local control of tumour if the normal tissue response was on the "toe" of a sigmoid dose-response curve while the tumour response was on the steeper middle part.

The differences in local control were small, and applied only to those patients who were in the "cords mobile" group. For these patients (40% of all the patients) the recurrence-free rates were 91% and 79% respectively at six years. We cannot estimate accurately what change in radiation dose would cause such an alteration in local control, because the five published dose response curves for local control

TABLE VI

Other late reactions

		Present		Absent		Not recorded	
All centres (years)		3F/wk	5F/wk	3F/wk	5F/wk	3F/wk	5F/wk
Patients analysed		299	326	299	326	299	326
Pain	½	23	18	264	293	12	15
	1	13	9	241	260	10	7
	2	4	7	191	210	11	8
	3	4	4	163	167	8	12
	4	2	3	121	136	11	6
	5	0	1	101	87	3	5
	6	0	2	66	49	3	4
Dysphagia	½	19	32	266	283	14	11
	1	13	20	240	247	11	9
	2	8	10	189	205	9	10
	3	4	6	162	166	9	11
	4	2	4	124	135	8	6
	5	2	0	99	88	3	5
	6	1	1	65	50	3	4
Probable myelitis	½	0	0	286	311	13	15
	1	1	1	254	265	9	10
	2	0	1	196	216	10	8
	3	0	0	167	172	8	11
	4	0	0	126	139	8	6
	5	0	0	101	88	3	5
	6	0	0	66	51	3	4
Perichondritis	½	4	8	278	299	17	19
	1	3	5	244	252	17	19
	2	0	2	183	205	23	18
	3	0	2	151	159	24	22
	4	0	1	117	128	17	16
	5	0	1	92	81	12	11
	6	0	1	59	45	10	9

TABLE VII

Necrosis

(a) Necrotic ulceration in normal tissue, confirmed on re-examination to have occurred in the absence of viable tumour tissue, and hence attributable to a total dose of radiation which exceeded normal tissue tolerance

Time of appearance	3F/wk	5F/wk
6 months	2 mucous membrane	1 mucous membrane
1 year	1 mucous membrane	0
2–6 years	0	0
Totals	3	1

(b) Necrosis reported initially, but viable tumour tissue identified subsequently

6 months	2 mucous membrane	1 mucous membrane
1 year	1 cartilage 2 mucous membrane	1 cartilage 2 mucous membrane 1 skin & mucous membrane
2 years	1 skin	0
3–6 years	0	0
Totals	6	5

of human tumours differ considerably (Shukovsky, 1970; Moench and Phillips, 1972; Shukovsky, 1974; Morrison, 1975; Stewart and Jackson, 1975). We can, therefore, only make rough estimates, and even these are made more uncertain by the fact that no published tumour response curve rises to 91%. Nevertheless, from the steepest curve (Stewart and Jackson, 1975) we can estimate that a change of 12% in local control is associated with only 3% alteration in dose. From the shallowest curve (Morrison, 1975) an alteration of 10% in dose appears to be required for this change in local control. The 3F/week doses used in this trial appear therefore to have been effectively 3 to 10% lower in biologically equivalent effect than the 5F/week doses, but this can be seen only in the patients in the "cord mobile" group, *i.e.* the early cases with a good prognosis. There was no identifiable difference in the effectiveness of the two fractionation schedules on tumours in the other sites. In no group or sub-group was the survival rate different for the two fractionation régimes.

Up to six years after treatment only 13 extra patients in the 3F/week group had had a local recurrence, which represents 2% of all the patients analysed but 9% of those with disease in the cords only. It seems possible that even these recurrences might have been prevented by a suitable small adjustment in the tumour dose for the early cases. Even if this adjustment is not made, this trial appears to justify the treatment of the advanced cancer patients on a 3F/week basis with the practical advantages that this offers to the individual patient.

CONCLUSIONS

When this trial was launched, in 1963, there were no precise data on which to base the dose to be used in each centre for the new fractionation régime as an alternative to the dose used in their established fractionation régime. An inspired guess had to be made, and now, 14 years later, it appears that any imbalance that may have been created thereby is small but may account for the differences which have been identified amongst the group of patients with the best prognosis.

These interim data are presented in sufficient detail for readers to draw their own conclusions, but the Working Party consider that, at the present time, the indications are that the treatment with 3F/week can be given safely, with all the advantages that this method has for the patient, to those with advanced disease. It remains an open question whether the differences noted between the patients with cancer confined to the vocal cords who were treated with 3F/week and those treated with 5F/week are due to the biological effectiveness of the dose level which was chosen for 3F/week having been lower than that chosen for 5F/week, or whether, indeed, there are other as yet unidentified factors which give rise to a better therapeutic ratio when treatment is given with 5F/week. The patients treated in this trial continue to be followed up and a more definite judgement may become possible when more data are available in subsequent years.

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Ioglycamide (Biligram) studies in man—plasma binding, renal and biliary excretion studies in jaundiced and anicteric patients*

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ABSTRACT

When five patients with varying degrees of hepatic impairment and a T-tube *in situ* were given intravenous ioglycamide at a rate of 2 mg/kg/min for two hours the mean biliary excretion in the first two hours was only 3.2% of the administered dose. In contrast, in five T-tube patients with relatively normal liver function the mean biliary excretion over the same time interval was 20.6%. The mean plasma concentration of ioglycamide achieved at the end of a two-hour intravenous infusion at 2 mg/kg/min was 1427 ± 187 μg/ml in six anicteric patients and 1262 ± 82 in six jaundiced patients. Despite these very similar plasma levels the 24-hour urinary excretion of ioglycamide was 42.3 ± 3.8% of the administered dose in the patients with jaundice compared with only 18.1 ± 2.4% in the anicteric group. These differences probably reflect the fact that the percentage of unbound contrast agent in the plasma of the jaundiced group (11.9 ± 1.9%) was significantly higher than that of the anicteric group (6.4 ± 0.9%). It is suggested that bilirubin and possibly other substances in the plasma are competing with ioglycamide for binding sites on albumin. These factors need to be borne in mind when performing intravenous cholangiograms on jaundiced patients.

The results of intravenous cholangiography in patients with impaired liver function tend to be poor. Recently there have been a number of studies in jaundiced patients reporting better results when a prolonged drip infusion technique was employed (Hoenig *et al.*, 1970; Martinez *et al.*, 1971; Voegeli, 1973; Pringot *et al.*, 1973; Fuchs and Preisig, 1975). Burgener and colleagues have the studied biliary and urinary excretion of iodipamide in normal and subsequently liver damaged dogs (Burgener and Fischer, 1975) and also in dogs with different degrees of common bile duct obstruction (Burgener *et al.*, 1975), but similar studies have not been carried out in man.

Using post-operative patients with a T-tube *in situ* we have compared the biliary excretion of ioglycamide achieved in five jaundiced subjects with that found in five anicteric subjects. We have also measured the renal excretion and plasma binding of ioglycamide in six normal and six jaundiced patients. This paper reports our findings.

MATERIALS AND METHODS

Studies of biliary ioglycamide concentration and secretion rates in patients with a biliary T-tube in situ

Anicteric patients—T-tube studies—Group A. Five patients who had undergone cholecystectomy and exploration of the common bile duct with insertion of a T-tube were studied. There were four female and one male patient in this group; the mean age was 58 years (range 43–76 years) and mean weight 63.4 kg (range 60–65 kg). All five patients had a T-tube cholangiogram performed on the seventh or eighth post-operative day. The T-tube was then clamped off for at least 48 hours before performing the experiment. At the time of study all patients had normal serum bilirubin level-mean 11.4 mmol/l (range 7–16 mmol/l). One of the patients (L.R.) had an elevated alkaline phosphatase level of 295 i.u./l (laboratory normal range 25–100 i.u./l), while the alkaline phosphatase level of the other four patients was within normal limits. At the start of the experiment the patient was placed in a comfortable recumbent position, the T-tube was unclamped and bile collected by gravity drainage. Two baseline ten-minute collections of bile were taken before starting the intravenous infusion of ioglycamide. Ioglycamide (Biligram, Schering Chemicals Ltd.) was then infused at a rate of 2 mg/kg/min for two hours using an Ivac 531 (Ivac Corporation, Middlesex, Harrow) infusion pump. Bile samples were collected every ten minutes throughout the two-hour ioglycamide infusion and stored at −20°C. The concentrations of ioglycamide in the T-tube bile was later analysed using a spectrophotometric method (Bell *et al.*, 1978). The amount of ioglycamide excreted into bile over the two-hour period of infusion was calculated by multiplying the concentration of contrast agent in each bile sample by its volume and adding the results of the 12 ten-minute sample together.

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*This work had received the approval of the St. Bartholomew's Hospital Ethical Committee and the informed consent of the patients was obtained before the investigations were performed.

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TABLE I

CLINICAL DETAILS OF FIVE JAUNDICED PATIENTS WITH A T-TUBE IN SITU

Name	Sex	Age	Serum Bilirubin (2–17 μmol/l)	Alk. Phos. (25–100 i.u./l)	Diagnosis
E.N.	F	59	27	348	Sclerosing cholangitis
M.S.	F	45	46	212	Intrahepatic cholestatic jaundice
D.R.	M	63	74	230	Ca C.B.D.
P.H.	M	68	116	226	Ca C.B.D.
A.T.	F	60	30	120	Choledocholithiasis

TABLE II

CLINICAL DETAILS OF SIX ANICTERIC PATIENTS USED IN THE IOGLYCAMIDE PLASMA BINDING AND RENAL EXCRETION STUDIES

Name	Sex	Age	Weight	Serum Bilirubin	Alk. Phos.	Diagnosis
C.B.	M	59	58	5	98	Ulcerative colitis, abdominal pain
G.G.	M	43	73	5	55	Abdominal pain, cholecystectomy, collagen disorder
A.M.	M	43	87	1	56	Ulcerative colitis, abdominal pain
J.P.	M	49	62	6	100	Depression, abdominal pain, hiatus hernia
J.B.	M	65	73	10	33	Hiatus hernia, bile
S.P.	M	65	73	3	72	Hypertension, abdominal pain, D.V.T.

Jaundiced patients—T-tube studies—Group B. This group consisted of three female and two male patients. Their ages, weights, liver function tests and clinical details are given in Table I. The T-tubes of E. H., M. S. and A. T. were clamped off for at least 48 hours before the ioglycamide infusion study and again the experiments were performed on the tenth or 11th post-operative day. P.H. and D.R. were both found to have inoperable carcinomas of the common bile duct. After insertion of the T-tube to relieve the obstructive jaundice the patients were left with either a complete (P.H.) of partial (D.R.) biliary fistula. P.H. was studied on the 13th post-operative day when his serum bilirubin had fallen from pre-operative levels of 400 μmol/l down to 116 μmol/l (normal range 2–7 μmol/l). D.R. was studied on the tenth post-operative day when the serum bilirubin had fallen from a pre-operative level of 306 μmol/l to 74 μmol/l. Like P.H., the T-tube of D.R. was not clamped off prior to the study.

Studies of plasma binding and renal excretion of ioglycamide in normal and jaundiced patients

Non-icteric patients—Group C. Six patients, all male, were studied. Their ages, weights, liver function tests and clinical details at the time of study are given in Table II. Potassium iodide (60 mg) was given to the patient on the night prior to the study to block thyroid uptake of iodine. The ioglycamide (two ampoules of 35% Biligram in 500 ml of normal saline) was labelled with 30 μCi ^{125}I ioglycamide and infused at a rate of 2 mg/kg body weight/min for two hours.

At the end of the two-hour infusion 10 ml of blood was taken into lithium heparin tubes. The blood samples were spun and the plasma removed. The plasma binding studies were usually carried out on the same day as the ioglycamide infusion. Where this was not possible the plasma samples were stored at 4°C and measured the following day. The total plasma concentration of ioglycamide achieved at the end of the two-hour infusion of contrast agent was estimated by measuring the radioactivity of 1 ml of the plasma in an ICN gamma set 500 and comparing it with that of 1 ml of the labelled stock ioglycamide solution.

Plasma binding studies

These studies were carried out using Perspex dialysis cells made by Mr. Roy Croxton in the Department of Pharmacology of St. Bartholomew's Hospital Medical School.

An aliquot of the patient's plasma ($\simeq$1.3 ml) was dialysed against an equal volume of normal saline

TABLE III

CLINICAL DETAILS OF SIX JAUNDICED PATIENTS USED IN THE IOGLYCAMIDE PLASMA BINDING AND RENAL EXCRETION STUDIES

Name	Sex	Age	Weight	Serum Bilirubin	Alk. Phos.	Diagnosis
H.B.	M	63	70	32	199	Choledocholithiasis
N.S.	F	54	72	116	231	Infective hepatitis with intrahepatic cholestasis
S.H.	M	57	76	57	143	CCF, gout, gallstones
P.H.	M	68	78	400	238	Ca. common bile duct
A.D.	M	48	100	340	305	Choledocholithiasis
T.B.	M	52	56	72	184	Alcoholic cirrhosis, chronic pancreatitis

TABLE IV

MEAN (± SEM) BILIARY IOGLYCAMIDE CONCENTRATIONS (MG/ML) IN FIVE ANICTERIC (GROUP A) AND FIVE JAUNDICED (GROUP B) PATIENTS INFUSED AT 2 MG/KG/MIN FOR TWO HOURS

Patient	Time in minutes from start of ioglycamide infusion											
	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	100–110	110–120
Group A	0	6.7 ± 1.6	12.3 ± 2.2	15.7 ± 2.8	17.8 ± 2.5	19.4 ± 2.4	20.8 ± 2.2	21.2 ± 2.5	23.5 ± 3.0	23.7 ± 2.6	23.8 ± 2.2	23.8 ± 2.2
Group B	0	0.6 ± 0.3	1.4 ± 0.7	2.8 ± 1.3	3.3 ± 1.4	3.6 ± 1.5	3.9 ± 1.6	4.7 ± 1.8	4.9 ± 1.8	6.2 ± 2.2	5.7 ± 1.8	5.8 ± 1.7

separated by a single thickness of Visking dialysis membrane (Scientific Supplies) which had previously been soaked in normal saline for about half an hour. The loaded cells were placed on a rotater (at$\simeq$20 revolutions per minute) in a humid oven at 37°C for 18 hours. It had previously been established that optimum time for dialysis by this method ranges between 13 and 20 hours. The radioactivity in 1 ml of the dialysis fluid was measured in the ICN gamma set and compared with that of 1 ml of the patient's whole undialysed plasma. The ratio of radioactivity in the dialysis fluid to the whole plasma multiplied by 100 gave the percentage of unbound or free ioglycamide in the plasma. All plasma binding studies were the mean of at least two and in some cases as many as five separate determinations.

Urinary excretion studies

The patient was asked to empty his/her bladder before the start of the ioglycamide infusion. The patients were encouraged to keep up a good fluid intake and all the urine collected over the first four hours was collected into one container, while all the urine passed in the next 20 hours was collected into a second container. The volume of urine passed in the two timed intervals was measured. The amount and concentration of ioglycamide excreted into the urine was calculated by comparing the radioactivity of the urine with that of the labelled stock solution.

Jaundiced patients—plasma binding and urinary excretion studies—Group D. Six patients, five male and one female, were studied. Ages, weights, liver function tests plus relevant clinical details are given in Table III. Ioglycamide labelled with 20 μCi of ^{125}I ioglycamide was infused at a rate of 2 mg/kg/min for two hours and a blood sample taken at the end of the infusion. Total plasma concentration and the percentage of free or unbound ioglycamide was estimated using the method described above.

The amount of ioglycamide excreted in the patient's urine over the first four hours and the ensuing 20 hours was also measured as described above.

RESULTS

Studies of biliary ioglycamide concentration and secretion in patients with a T-tube in situ

Anicteric patients—T-tube studies—Group A. The mean biliary ioglycamide concentration of the five patients studied is shown in Table IV. The contrast medium started to appear in bile in the second ten-minute period after starting the intravenous infusion of ioglycamide. The concentrations then rose rapidly over the next four ten-minute collection periods before reaching a plateau. The ioglycamide levels in the last four samples (*i.e.* between 90 and 120 minutes) were very similar. The lowest biliary concentrations were seen in L.R., the only patient with a raised alkaline phosphatase level. Table V shows the mean number of mg of ioglycamide administered intravenously to the patients over the two hours, plus the mean number of mg of the contrast agent excreted into the patients' bile over the same time interval. The mean biliary excretion of ioglycamide over the two hours of the infusion (expressed as a percentage of the administered dose) was 20.6 ± 3.2%.

Jaundiced patients—T-tube studies—Group B. The mean biliary ioglycamide concentrations of the five patients studied is shown in Table IV. The concentrations are, not surprisingly, much lower than those of the anicteric group. However, like these patients,

TABLE V

Total dose of ioglycamide (mean ± SEM) given to the five anicteric patients (Group A) and five jaundiced (Group B) patients. The percentage of the administered dose excreted into bile over two hours is also shown

Patient	Weight	Total dose given i.v. (mg)	Mg excreted into bile in two hours	% excretion
Group A	63.4 ± 0.9	15,216 ± 223	3,154 ± 504	20.6 ± 3.2
Group B	58.8 ± 6.4	14,112 ± 1,528	449.0 ± 279	3.2 ± 1.7

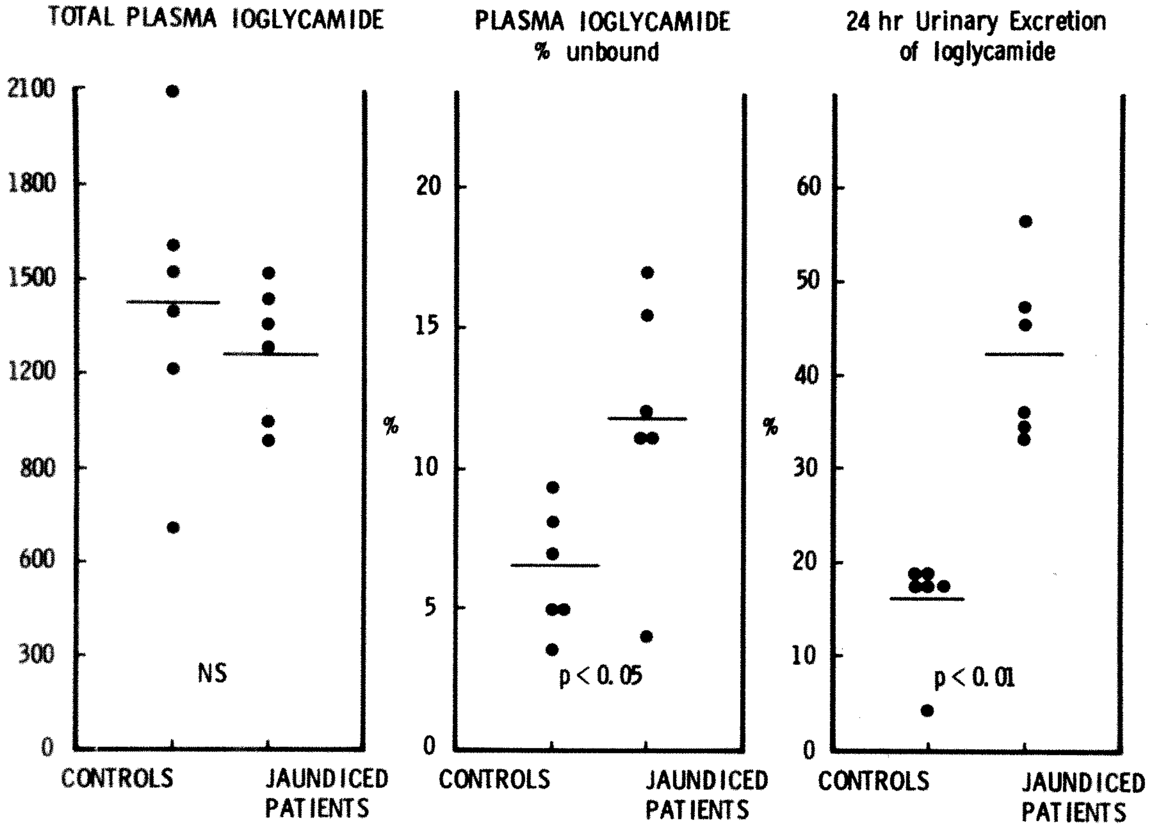

Fig. 1.

Six anicteric (Group C) and six jaundiced (Group D) patients received intravenous ioglycamide at a rate of 2 mg/kg/min for 120 minutes. The total plasma concentration of the contrast agent achieved at the end of two hours is shown in the left hand diagram. The percentage of the plasma ioglycamide in the unbound form is shown in the centre figure, while the percentage of the administered dose excreted by the kidneys over 24 hours is shown in the right hand diagram.

the biliary concentration appeared to level off between 90 and 120 minutes. In all cases the concentration of iodine achieved in the bile was well below the 1% (≡20 mg ioglycamide/ml bile) required for satisfactory opacification of the bile duct (Edholm and Jacobson, 1959). The lowest biliary concentration of ioglycamide was seen in the patient with the highest serum bilirubin (P.H.).

Table V shows the mean number of mg of ioglycamide administered intravenously to each patient over the two-hour infusion period plus the mean number of mg of contrast agent excreted into the patients' bile over the same time interval. The mean biliary excretion of ioglycamide over the two hours of the infusion (expressed as a percentage of the administered dose) was 3.2±1.7%.

Studies of plasma binding and renal excretion of ioglycamide in normal and jaundiced patients

Non-icteric patients—Group C. The mean total ioglycamide concentration achieved in the plasma at the end of the two-hour infusion of contrast agent was 1427±187 μg/ml. The mean percentage of unbound ioglycamide in this group was 6.4±0.9%. The urinary excretion of ioglycamide (expressed as a percentage of the administered dose) was 10.9±1.6% in the first four hours and 18.1±2.4% in 24 hours. The total number of mg of ioglycamide passed in the urine over the first four hours and in the complete 24 hour period were 1825±275 and 2498±394 mg respectively.

Jaundiced patients—Group D. The mean total ioglycamide concentration achieved in the plasma at the end of the two-hour infusion of contrast agent was 1262±84 μg/ml. These levels were not significantly different from those in Group C (see Fig. 1). The mean percentage of free or unbound ioglycamide in Group D was 11.8±1.9%. This was significantly higher ($p < 0.05$ using Wilcoxon's sum of ranks test) than that found in Group C (see Fig. 1). The serum albumin in the Group D patients was 31.2±1.3 g/l which was not significantly lower than that of Group C (34.0±0.8 g/l). The urinary excretion of ioglycamide (expressed as a percentage of the administered dose) was 16.4±2.6% in the first four hours and 42.3±3.8% in 24 hours (see Fig. 1). The total number of mg of ioglycamide passed in the urine over the first four hours and over the complete 24-hour period was 2858±447 and 7720±897 mg respectively. The total and the percentage urinary excretion of ioglycamide in Group D were both significantly higher ($p < 0.01$ using Wilcoxon's sum of ranks test) than those in Group C (see Fig. 1).

Discussion

The structure of ioglycamide is very like that of the other commonly employed cholangiographic agent, iodipamide. The renal and hepatic handling of these two compounds is probably very similar (Sperber and Sperber, 1971). Following intravenous administration the contrast agents are reversibly bound to albumin (Lasser *et al.*, 1962; Lang and Lasser, 1967). The evidence for iodipamide suggests that only the protein-bound fraction in the blood is taken up by the hepatocyte to be actively excreted into the bile, whereas the unbound portion is available for glomerular filtration (Leupold and Heuck, 1957).

We found a significant increase in the percentage of ioglycamide in the free (unbound) form in Group D patients. This probably reflects competition by other substances for albumin binding sites. Bilirubin can certainly displace phenytoin from its binding sites on human albumin (Coutinho *et al.*, 1973; Odell, 1973; Rane *et al.*, 1971), as can free fatty acids (Spector and Santor, 1973; Fredholm *et al.*, 1975). Both these substances are known to be elevated in patients with hepatic dysfunction and may reduce the number of albumin binding sites available to ioglycamide.

In the kidney, the excretion of biliary contrast agents is predominantly by glomerular filtration with urinary excretion being directly proportional to plasma concentration (Fischer, 1965; Loeb *et al.*, 1975). It is, however, only the small proportion of the plasma ioglycamide present in the unbound form which is available for glomerular filtration (Leupold and Heuck, 1957). The plasma half-life of biliary contrast agents are prolonged in the presence of impaired hepatic function (Burgener and Fischer, 1975). This factor plus diminished plasma binding (see above) probably explains the enhanced renal elimination of ioglycamide noted in Group D patients. It also, incidentally, helps to explain why the renal tract is so frequently visualized radiologically when a jaundiced patient undergoes intravenous cholangiography.

Previous experimental work in animals has shown that the hepatic excretion of both iodipamide and ioglycamide are subject to a transport maximum (Tm))Miller *et al.*, 1969; Hoenig and Preisig, 1973; Burgener *et al.*, 1970; Whitney and Bell, 1976). Most organic anions which are excreted in the bile probably share the same active secretion mechanism (Sperber and Sperber, 1971). Among the many compounds handled by this mechanism are cholecystographic agents, bromsulphthalein (BSP), bilirubin, porphyrins and the glucuronide esters of various substances (Sperber and Sperber, 1971).

Thus in the jaundiced patient the concentration of many of these substances may be considerably elevated and hence compete with ioglycamide for biliary excretion.

With these factors mitigating against the successful transfer of biliary contrast agents from plasma to bile it is not surprising that cholangiography is often unsuccessful in jaundiced patients. In none of our five patients in Group B was the concentration of ioglycamide, and thus iodine, in the T-tube bile sufficient for radiological opacification (Edholm and Jacobson, 1959). Recently, prolonged drip infusion cholangiography has been used in an attempt to overcome these problems (Fuchs and Preisig, 1975). The hope is that when there is a sustained high plasma concentration of ioglycamide, molecules of the contrast agent, rather than those of any competing substance will be excreted by the liver. In our Groups A and B patients the biliary concentration of ioglycamide appeared to plateau by two hours and it is doubtful if further prolongation of the infusion time would have resulted in sufficient enhancement in the levels of contrast agent to make the patients' bile ducts visible radiologically. Certainly experimental work in dogs with either partially obstructed common bile ducts (Burgener *et al.*, 1975) or parenchymal liver damage (Burgener and Fischer, 1975) failed to show any advantage in prolonged infusion.

On the basis of our results we conclude that further advances in intravenous cholangiography in the jaundiced patient are more likely to come from the introduction of new and more competitive contrast agents than from modifications of infusion technique.

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Endoscopic and radiological assessment of recurrent ulceration after peptic ulcer surgery

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ABSTRACT

One hundred and eighteen patients with dyspepsia after peptic ulcer surgery were assessed by a double contrast barium meal and fibre-optic endoscopy, for the possibility of recurrent ulceration. There was overall endoscopic-radiological agreement in 89%. It is concluded that the two techniques are complementary and that a double contrast barium meal performed and interpreted by an experienced radiologist can demonstrate the presence or absence of a recurrent peptic ulcer with an acceptable degree of accuracy.

The recurrence of dyspeptic symptoms after peptic ulcer surgery is a disappointment for both patient and doctor. The key to effective management in this situation is to establish whether a recurrent ulcer is the explanation for the patient's complaints and clinical assessment can do no more than suggest this possibility.

The conventional barium meal is notoriously inaccurate in the post-operative situation (Schulman, 1971) and fibre-optic endoscopy has justifiably come to be regarded as the investigation of choice for this purpose (Cotton *et al.*, 1973).

However, comparative endoscopic-radiological studies have shown that when a double contrast method is employed for the barium meal, a high degree of diagnostic accuracy can be achieved in the un-operated stomach (Salter, 1975; Rogers *et al.*, 1976; Herlinger *et al.*, 1977). The aim of this investigation was to assess the diagnostic value of the double contrast method in the post-operative situation.

PATIENTS AND METHODS

This prospective study was commenced in June 1973. All symptomatic patients after previous peptic ulcer surgery referred to a combined gastroenterology clinic (Salter *et al.*, 1975) were included, and after a thorough clinical assessment a double contrast barium meal was performed. The patient was then submitted to endoscopy of the upper gastrointestinal tract within four weeks of the barium meal examination.

The double contrast barium examinations were all performed by experienced consultant radiologists. The method, which has been described elsewhere (Scott-Harden, 1973), is that used in this hospital in routine investigation of the upper gastrointestinal tract with an important modification designed to overcome the particular problem of the rapid escape of the distending gas through a stoma or a freely open pylorus after pyloroplasty. This was achieved by encouraging the patient to sip through a straw an effervescent drink of high gas content during the whole period of the examination.

All the endoscopies were performed by a consultant physician (R.H.S.) who was aware of the barium meal result. The relevant films were also reviewed with a radiologist before each endoscopic examination and a definitive statement recorded as to whether or not an ulcer was demonstrated radiologically. The endoscopies were performed using an endviewing Olympus gastrointestinal fibrescope and no premedication or pharyngeal anaesthesia was employed. Each patient was given an intravenous injection of 40 mgms of hyoscine-N-butylbromide and the minimum of intravenous diazepam sufficient to allay excessive apprehension (rarely more than 10 mgms) at the start of the examination.

The total number of patients included in this series was 118 (86 male – 32 female). The age range was 17 to 71 years with the average being 49 years. The original pre-operative diagnoses were—duodenal ulcer 93 patients, gastric ulcer 15 patients, combined duodenal and gastric ulceration four patients and pre-pyloric ulceration six patients. The previous operative procedures included gastroenterostomy, truncal vagotomy and gastroenterostomy or pyloroplasty, vagotomy and antrectomy and Billroth I or Polya gastrectomy.

RESULTS

The detailed results of the comparative radiological and endoscopic findings in the various post-operative situations are summarized in Tables I and II.

In the series of 118 patients, a definite radiological diagnosis of recurrent peptic ulceration (whether anastamotic, gastric or recurrent duodenal) was

TABLE I

COMPARISON OF THE INCIDENCE OF RECURRENT ULCER AS DEMONSTRATED BY RADIOLOGY AND ENDOSCOPY AFTER GASTROENTEROSTOMY AND VAGOTOMY AND DRAINAGE PROCEDURES

Surgical procedure	Total no. of patients	Radiology		Endoscopy	
				Ulcer	No ulcer
Gastro-enterostomy	9	Ulcer	2	2	0
		No ulcer	7	0	7
Vagotomy and pyloroplasty	39	Ulcer	12	10	2
		No ulcer	27	3	24
Vagotomy and gastro-enterostomy	17	Ulcer	4	3	1
		No ulcer	13	1	12
Vagotomy, pyloroplasty and gastro-enterostomy	7	Ulcer	0	0	0
		No ulcer	7	0	7

TABLE II

COMPARISON OF THE INCIDENCE OF RECURRENT ULCER AS DEMONSTRATED BY RADIOLOGY AND ENDOSCOPY AFTER ANTRECTOMY AND GASTRECTOMY

Surgical procedure	Total no. of patients	Radiology		Endoscopy	
				Ulcer	No Ulcer
Vagotomy and antrectomy	5	Ulcer	0	0	0
		No ulcer	5	0	5
Billroth I gastrectomy	12	Ulcer	4	4	0
		No ulcer	8	0	8
Polya gastrectomy	29	Ulcer	4	2	2
		Possible ulcer	4	0	4
		No ulcer	21	0	21

made in 26. Twenty-one of these were confirmed at endoscopy and five proved to be endoscopy negative. The possibility of a stomal ulcer was reported in four patients after Polya gastrectomy and none of these were confirmed at endoscopy.

Of the 88 patients in whom the barium meal was negative, 84 were negative endoscopically and an ulcer was detected in four.

There was overall endoscopic-radiological agreement in 105 of the 118 patients in the series (89%) and if only those with a definitive radiological diagnosis are included (114) the radiological-endoscopic correlation was 92%.

The incidence of radiological false positives and radiological false negatives was 7.6% and 3.4% respectively.

DISCUSSION

Fibre-optic endoscopy of the upper gastrointestinal tract has justifiably come to be regarded as the investigation of choice in patients with recurrent dyspepsia after peptic ulcer surgery. The conventional barium meal has little to offer in this situation (Schulman, 1971; Cotton *et al.*, 1973) but the overall 89% agreement between endoscopy and double contrast radiology in this series of post-operative patients is not significantly different from our experience in the pre-operative situation (Salter, 1975).

Possible explanations for the radiological-endoscopic discrepancy are:

1. A lesion demonstrated radiologically may be missed at endoscopy. We do not regard endoscopy as infallible and problems such as bile reflux, difficulty in obtaining adequate gastric distension, anatomical distortion and patient restlessness may contribute to the endoscopist's difficulties. Unfortunately we have no check on the endoscopist's performance other than the knowledge that all the patients in whom a recurrent ulcer was confirmed at endoscopy were subsequently submitted to further surgery and the presence of an ulcer confirmed at laparotomy. Only seven of the endoscopy negative patients were submitted to surgery (for gallstones or bile vomiting) and in none was an ulcer discovered at laparotomy.

2. An error in the interpretation of the barium meal films (observer error). The accurate reporting of double contrast barium meal films in the post-operative situation requires considerable experience and to this end the radiologists have undoubtedly found it valuable to attend the endoscopy sessions. Errors of interpretation accounted for the majority of the radiological-endoscopic discrepancies and the radiological interpretation was more accurate towards the end of the series.

3. Failure of the radiological technique to establish whether or not an ulcer was present. This accounted for a minority (8%) of the radiological-endoscopic discrepancies and it can be seen that a

particularly difficult area was the demonstration or otherwise of a stomal ulcer after Polya gastrectomy.

In conclusion, we feel that the double contrast barium meal is a valuable part of the assessment of symptomatic patients following peptic ulcer surgery. Although this contribution has been concerned with the establishment or otherwise of a recurrent ulcer, the double contrast technique, which is a quick and well-tolerated procedure, also provides useful information as to the presence of an hiatus hernia with or without gastro-oesophageal reflux, and a possible gastric neoplasm. Facilities for endoscopic examination of the upper gastrointestinal tract are now available at most district general hospitals, but even when this is the case, this technique should be regarded as complementary to the double contrast barium meal. If the facilities for endoscopy are not available or, for various reasons, this technique is either contra-indicated or impossible, a double contrast barium meal performed and interpreted by an experienced radiologist can predict the presence or absence of a recurrent peptic ulcer with an acceptable degree of accuracy.

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Book review

Radiological atlas of common diseases of the small bowel. By J. L. Sellink. pp. 392, 1976 (The Netherlands; H. E. Stenfert Kroese B. V. Leiden), Dfl. 168.

In 1969 Professor J. R. Von Ronnen, head of the Department of Radiology at the Leiden University Hospital, asked one of his younger colleagues, Dr. J. L. Sellink, to determine whether it was possible to improve the disappointing results then being obtained by conventional barium examinations of the small bowel. During the next few years Dr. Sellink concentrated on improving the technique of examination of the small intestine following duodenal intubation. The initial results were published in a book in 1971. Since then he has refined his technique and acquired a vast experience covering virtually all forms of pathology of the small bowel. Many radiologists have visited his department in order to study his technique and benefit from his teaching and experience.

The "Radiological Atlas of Common Diseases of the Small Bowel" is based on a selection of the radiographs of patients examined between 1970 and 1974. The book, however, is much more than an atlas and describes many conditions which are far from common.

The first chapters describe the anatomy and physiology of the small intestine in some detail. There is then a detailed description of the properties of contrast medium and the way in which variations can cause alteration in the radiological appearances. He then gives a historical review of the different methods that have been employed over the years for the examination of the small bowel, including the use of drugs to alter the rate of transit with an account of their uses and limitations. One of the most interesting sections of the book is a detailed description of the exact sequence of events which should be followed if the small bowel infusion is to be successful. The normal appearances and the variations are described, as well as some of the misleading appearances which may deceive due to faults in technique.

The main part of the book consists of illustrations and descriptions of the appearances seen in a variety of conditions including inflammatory diseases, tumours, vascular disorders, disturbed motility and congenital abnormalities. The quality of the illustrations is excellent.

This is an outstanding book which should be read by all radiologists interested in the small bowel. It is obviously the work of an enthusiast who by his meticulous work has gone a long way towards correlating the radiological appearances seen on small bowel examination with the underlying pathological conditions.

J. W. Laws.

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The importance of the anomalous left gastric artery in the arteriography of gastric haemorrhage

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ABSTRACT

The importance of the occasional anomalous origin of the left gastric artery (LGA) from the aorta in the arteriographic evaluation of gastrointestinal haemorrhage is illustrated by two cases. The incidence of the anomaly is between 2.5 and 5.4% and should be considered when the LGA is not opacified on a coeliac arteriogram.

Angiography has become a dependable method for localization and treatment of gastrointestinal haemorrhage (Nusbaum *et al.*, 1969). Variations in the arterial blood supply to the distal oesophagus and proximal stomach should be familiar to all angiographers.

The communication describes two patients in whom gastric bleeding was detected by catheterization of the left gastric artery arising anomalously directly from the aorta.

CASE REPORTS

Case 1

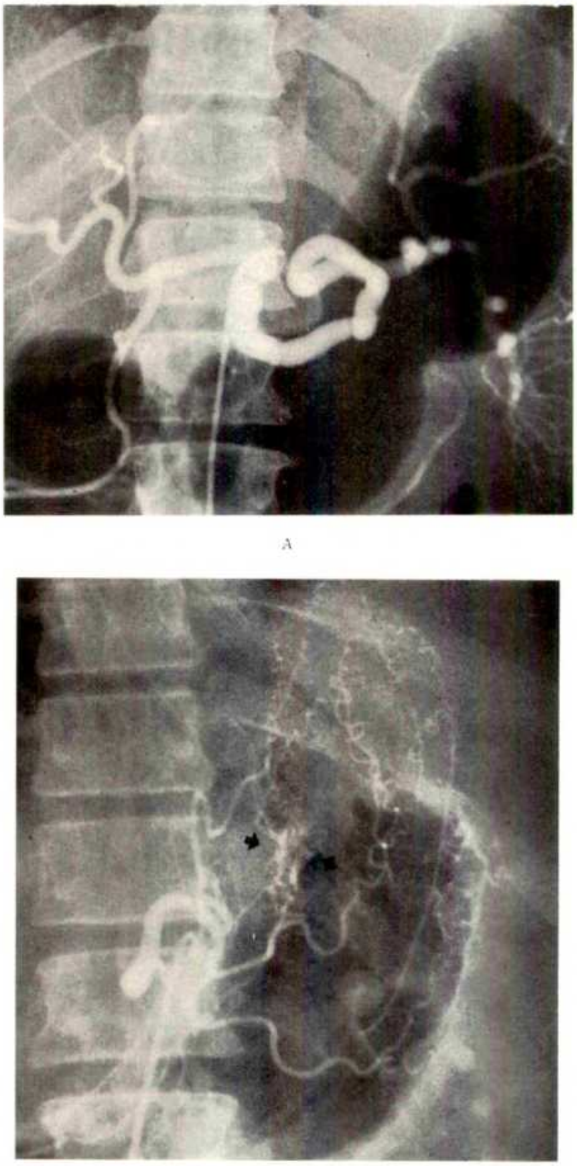
A 55-year-old man with stage IV-B Hodgkin's disease was being treated with chemotherapy when he developed massive upper gastrointestinal bleeding. A coeliac arteriogram failed to disclose the bleeding site (Fig. 1); however, the LGA was not opacified. An abdominal aortogram demonstrated that the LGA arose directly from the aorta above the coeliac orifice. Selective injection of the LGA demonstrated active bleeding which was controlled by vasopressin infusion.

Case 2.

A 32-year-old man presented with massive upper gastrointestinal bleeding which was uncontrolled medically. Gastroscopy demonstrated a bleeding gastric ulcer. Since the patient refused surgery, arteriography was undertaken for possible therapy. The LGA was found to arise directly from the aorta (Fig. 2). A small pseudo-aneurysm of a tertiary gastric arterial branch and contrast extravasation were demonstrated. The bleeding could not be controlled with vasopressin infusion. Because of fear of reflux into the aorta, embolization was not attempted. The patient was convinced surgery would be necessary and it was carried out successfully.

DISCUSSION

Opacification of the LGA is important in the arteriographic evaluation of patients with upper gastrointestinal bleeding, since the majority of distal


A

B

FIGURE 1.

(A) A selective coeliac arteriogram fails to demonstrate a bleeding site, but the LGA is not opacified.

(B) A selective injection of the replaced LGA demonstrates the site of bleeding in the stomach (arrows).

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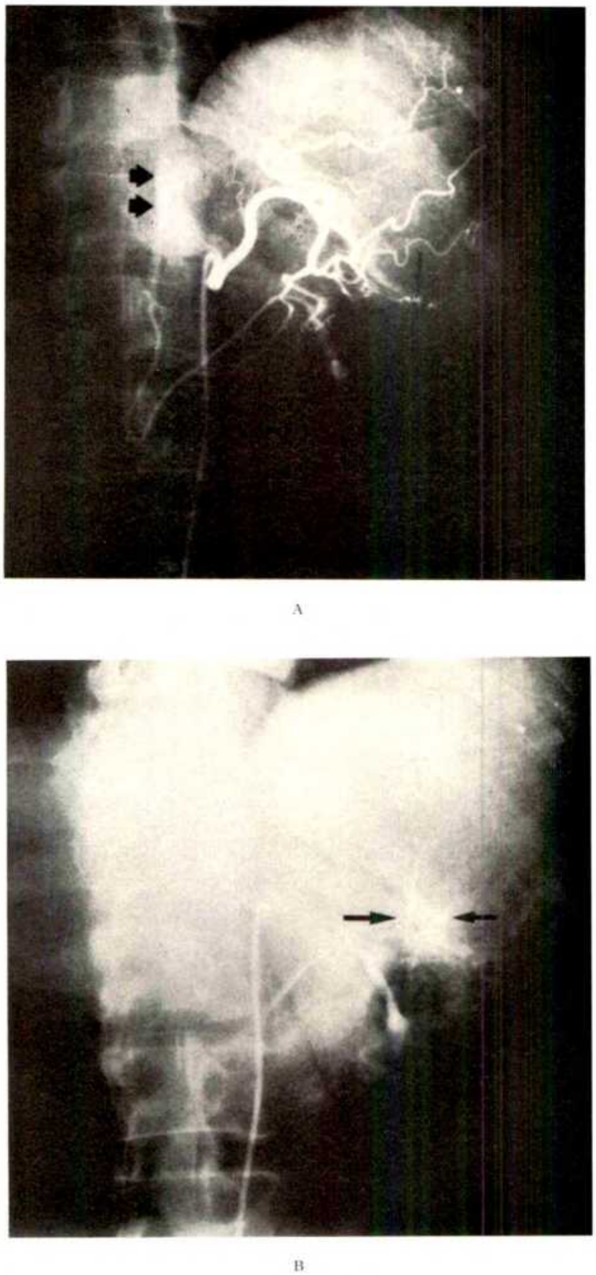

FIGURE 2.

(A) Injection of the replaced LGA demonstrates a small pseudoaneurysm of a tertiary branch (vertical arrow) and early contrast extravasation into the gastric lumen. Note contrast refluxing into the aorta (horizontal arrows), proving separate origin of the artery from the aorta. The right gastric artery is filled retrogradely.

(B) In the capillary phase there is a frank contrast accumulation in the gastric lumen.

oesophageal and gastric bleeding sites lie within the distribution of this artery (Athanasoulis, 1976). This is usually accomplished quite easily by a coeliac arteriogram. There has been only one previous report of angiographic identification of a bleeding site by selective catheterization of a LGA arising directly from the aorta (Thompson *et al.*, 1975).

Failure to opacify the LGA on a coeliac arteriogram may be caused by: (1) too distal positioning of the catheter, (2) occlusion of the LGA at its origin or (3) anomalous origin of the LGA from the aorta. The first may be corrected by a more forceful injection which fills the coeliac trunk to the aorta. In the second instance, the occluded LGA will usually be opacified retrogradely from an enlarged right gastric artery. Lastly, anomalous origin of the LGA from the aorta may be detected by aortography or direct catheterization above the coeliac origin, usually within one cm.

The incidence of this anomaly of the LGA is between 2.5% (Michels, 1955) and 5.4% (Sundgren, 1970). In Sundgren's series, the inferior phrenic artery originated from eight of ten anomalous LGAs. The inferior phrenic artery is the source of bleeding from the gastroesophageal junction in an occasional patient (Thompson *et al.*, 1975).

Catheterization of this anomalously arising artery is usually quite easy with a commercially available cobra-shaped catheter.

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Protection of the eye during carotid angiography

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ABSTRACT

An eye shield was developed for use in neurological examinations in projections in which it does not interfere with the information sought. Use of this shield in A.P., oblique, 30 deg Towne's and 12 deg carotid Towne's projections reduced the corneal dose to approximately 5% of the unshielded value. For lateral projections, doses were reduced to approximately 5–15%. Use of the shield resulted in corneal doses of the order of 0.5 mrad/mAs and 1.0 mrad/mAs for standard and magnified projections respectively, with the exception of the lateral projections for which the corresponding values were approximately 0.3 mrad/mAs and 0.7 mrad/mAs. Corneal dose for a typical carotid angiogram was estimated to be reduced from 6.2 rad to 0.33 rad by the use of the shield.

Results of radiation dose measurements to the eye during neuro-radiological examinations have been published by Chin *et al.*, (1970), Bergstrom *et al.*, (1972), Isherwood *et al.* (1975), Smith *et al.* (1976). These authors have shown that, without any form of protection, radiation doses of many rads may be received by the cornea and lens. Whilst doses are generally less than 20 rad for the examinations investigated, Isherwood *et al.* (1975) estimated that extensive neuro-radiological procedures could lead to a cumulative dose of the order of 60 rad. The use of corneal protection has been recommended by most authors, and shields have been described by Chin *et al.* (1970) and Bergstrom *et al.* (1972) which give a reduction of dose to approximately 10% of the unshielded value.

The purpose of this note is to describe a simple shield developed at Royal Perth Hospital which reduces corneal doses received from projections used in carotid angiography to typically 5% of the unshielded value.

THE EYE SHIELD

The shield consists of a lead moulding, shown diagrammatically in Fig. 1, contoured to the "normal eye" as determined by shaping the prototype to a radiotherapy face mask. It extends from just below the supra-orbital ridge to the inferior orbital margin, and from the medial canthus to beyond the lateral canthus, thus encapsulating the anterior/oblique/lateral aspect of the orbit. A high level of protection is thereby afforded, together with ease of positioning. The thickness varies from 1.5 mm at the edge rising sharply to 10 mm at the centre as a result of the casting sprue, which thus provides a convenient

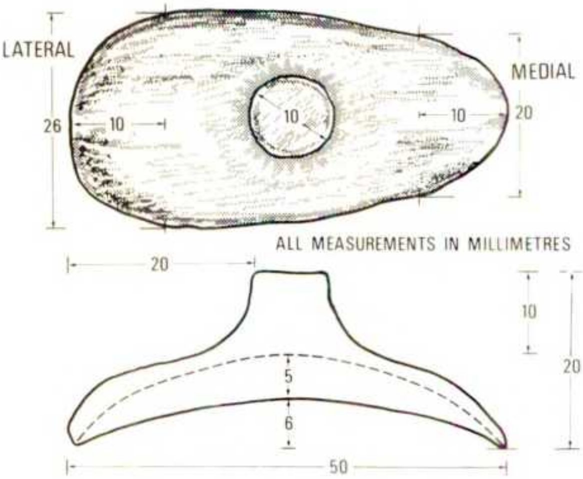

FIG. 1.

Plan and elevation of the eye shield.

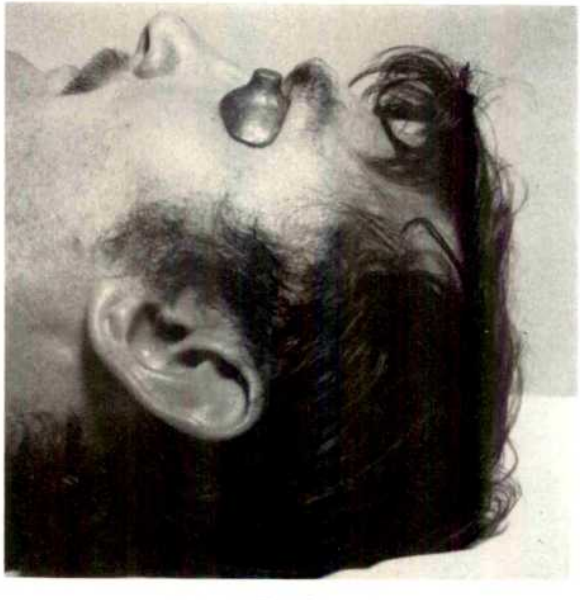

FIG. 2.

Shield in position on supine patient

lifting handle as well as affording additional protection directly over the cornea. At the minimum thickness of 1.5 mm of lead, the direct transmission of 80 kV, 2.8 mm Al HVT X rays is only of the order of 0.02% and the transmitted radiation dose is consequently effectively negligible in comparison with that received at the cornea from internal scatter. The shield weighs 35 g and is well tolerated due to the weight being distributed over a relatively large contact area with correspondingly low pressure. No discomfort has yet been reported by the several hundred patients on whom it has so far been used. The weight is also sufficient to render the shield self-retaining whilst the patient is in the supine position (Fig. 2), and it is only when the subarachnoid structures are of interest, when the head is rotated some 45 deg, that the shield requires to be taped in position using surgical tape. In this oblique projection, the eye closer to the tube cannot of course be protected. Similarly, during the A.P. or 12 deg fronto-occipital (carotid Towne's) series, the eye on the side under investigation cannot be protected, whereas both eyes may be shielded during the lateral series. On those occasions when the cervical portions of the arteries require to be visualized it is customary to protect both eyes.

MEASUREMENTS

Measurements were made to determine the ratio of the unshielded to shielded corneal dose and the magnitude of the latter. The ratio thus determined increased with improved shielding efficiency. Three series of measurements were made using a phantom, patients and cadavers. The phantom consisted of a 17 cm diameter water-filled polythene bottle on to the surface of which a protruberance of bone wax in the shape of an orbit was attached. Other measurements were made on a total of 20 patients but difficulties were experienced in the interpretation of the results in a number of cases because the orbit had not been in the beam. Also, some projections were not used in the examinations investigated. The patient measurements were consequently supplemented by others on three cadavers under controlled conditions in which all projections were used.

All measurements were made with LiF thermoluminescent dosimeters (TLD) in the form of discs 12.7 mm diameter by 0.4 mm thick. The TLDs were calibrated on a Mix D phantom using a 2.8 mm Al HVT X-ray beam, corresponding approximately to an 80 kV, 3.2 mm Al total filtration diagnostic beam. Read-out was performed on a Teledyne Isotopes Model TLD 7300 using nitrogen purging

TABLE I

EFFECTIVENESS OF EYE-SHIELD AND CORNEAL DOSES OBTAINED WITH ITS USE

Projection	Factors			Shielding ratio*			Shielded corneal dose* mrad/mAs	
	kV	mAs/exposure	f.s.d.	Phantom	Patient	Cadaver	Patient	Cadaver
A.P.								
Standard	75	28	80	10.4 ± 2.4	15.4 ± 1.6	17.9 ± 3.0	0.55 ± 0.08	0.55 ± 0.16
Magnified	80	16	50	9.8 ± 0.9		25.8 ± 2.4		1.14 ± 0.24
Lateral								
Standard†	68	28	85	3.5 ± 0.6	(a) 13.5 ± 2.3	(a) 20.4 ± 4.7 (b) 2.8 ± 1.1	(a) 0.26 ± 0.07	(a) 0.36 ± 0.08 (b) 0.18 ± 0.04
Magnified†	88	16	70	7.7 ± 0.9		(a) 6.5 ± 4.4 (b) 2.0 ± 2.0		(a) 0.70 ± 0.32 (b) 0.47 ± 0.15
Oblique	75	28	80	8.9 ± 0.4		23.1 ± 2.3		0.40 ± 0.08
30 deg Townes	80	28	80	7.4 ± 1.0	18.3 ± 3.4	17.0 ± 4.8	0.50 ± 0.10	0.63 ± 0.14
12 deg Carotid Townes								
Standard	75	28	80	8.9 ± 0.2		19.4 ± 3.6		0.54 ± 0.13
Magnified	80	28	55	10.0 ± 1.0		25.4 ± 5.4		0.97 ± 0.12

*For both eyes, except in lateral projections. Results given with their standard deviations. (Shielding ratio = unshielded/shielded dose)

†(a) eye nearest tube

†(b) eye remote from tube.

and the standard annealing cycle given by the instrument. Disc sensitivities were checked at 0, 45 and 90 deg incidence on the surface of a block of Mix D, and no significant variation with angle was found. Discs were taken from the batch as supplied and tests showed that the accuracy of dose measurement increased from ±20% at 200 mrad to ±14% at 1 rad. Unshielded corneal doses were, generally, considerably greater than 1 rad and the shielded doses measured were less than 200 mrad in only a few cases. Patient and cadaver measurements were made with the TLDs positioned on the eyelid and results have been reported in mrad in tissue per milliampere-second. Bergstrom *et al.* (1972) have shown that there is no difference in dose between the eyelid and cornea.

Radiological factors representative of those used in examinations were chosen for the cadaver measurements and are shown in Table I. The low values of mAs per exposure result from the use of a high speed combination of Siemens special Puck intensifying screens with Agfa Curix RPI film.

Results and Discussion

The results are shown in Table I. It can be seen that the shielding ratios obtained with the water phantom were lower than those obtained with humans. This was due to the higher shielded doses measured on the phantom and was attributed to the absence of the attenuation given by the bony structures of the skull. The results have been included to illustrate the error possible with the use of a simple phantom in this particular case.

With the exception of the lateral projections, the shielded corneal doses were approximately 0.5 mrad/mAs and 1.0 mrad/mAs for the standard and magnified projections respectively. The corresponding values for the lateral projections were lower, reflecting the effects of the differing exposure factors between A.P. and lateral projections, rather than indicating an improved efficiency of the shield in this projection; in fact, a decreased efficiency could be anticipated.

It is probable that, at least in the magnified A.P. and Towne's projections, the shielding ratios should have been greater than for the standard projections. This could arise because of the shadowing effect of the shield moving the edge of the scattering volume in the head away from the cornea as the tube target-skin distance was reduced. Consequently, the scattered radiation dose might be expected to increase more slowly than the primary beam dose on the surface, leading to an increase in the observed shielding ratio. However, the standard deviations of the results were too high to permit firm conclusions to be drawn on this point.

The shielding ratios obtained for the lateral projections with the cadavers appear anomalous. It would be expected that, in general, the shield would be less effective in this type of projection where it is end-on to the beam. Also, depending on the detailed positioning of the shield and TLD and the angulation of the beam, it is conceivable that the TLD may receive attenuated primary and forward scattered radiation in addition to scatter from other directions. This may be particularly true with magnified views using short target-skin distances. These factors make interpretation of the lateral projection results difficult and, as can be seen in Table I for the eye nearest the tube, whilst an apparently high shielding ratio was found in the standard projection, a low ratio with a 68% standard deviation was found in the magnified projection. Shielding ratios were lower for the eye remote from the tube because the surface dose was much lower at this point than for the other eye, whilst the scattered radiation doses were reduced to a lesser degree.

The data of Table I may be used to estimate the corneal doses delivered during a typical carotid angiographic examination with and without the use of an eye shield. For an examination consisting of eight A.P., eight carotid Towne's, and eight lateral exposures, with the factors as shown in Table I, the total doses to the cornea nearest the tube would be 0.33 rad and 6.2 rad with and without shielding respectively. Results were calculated using data from the cadaver measurements in Table I.

Acknowledgments

A number of the members of the staff of Royal Perth Hospital assisted with the reported investigation, and particular acknowledgment should be made of contributions from Mr. P. Klemp and Mr. G. Stone, Department of Medical Physics, Mr. E. Woodcock of the Maxillary Facial Laboratory and Dr. L. R. Finlay-Jones and Mr. B. Clarke of the Department of Pathology.

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A computer simulation study of optimal thyroid radiation protection during investigations involving the administration of radioiodine-labelled pharmaceuticals

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ABSTRACT

The administration of iodide for thyroid blocking is now known to carry its own risks, at least in certain categories of patients. We have therefore made a theoretical study by computer simulation of the efficacy of various thyroid blocking regimes.

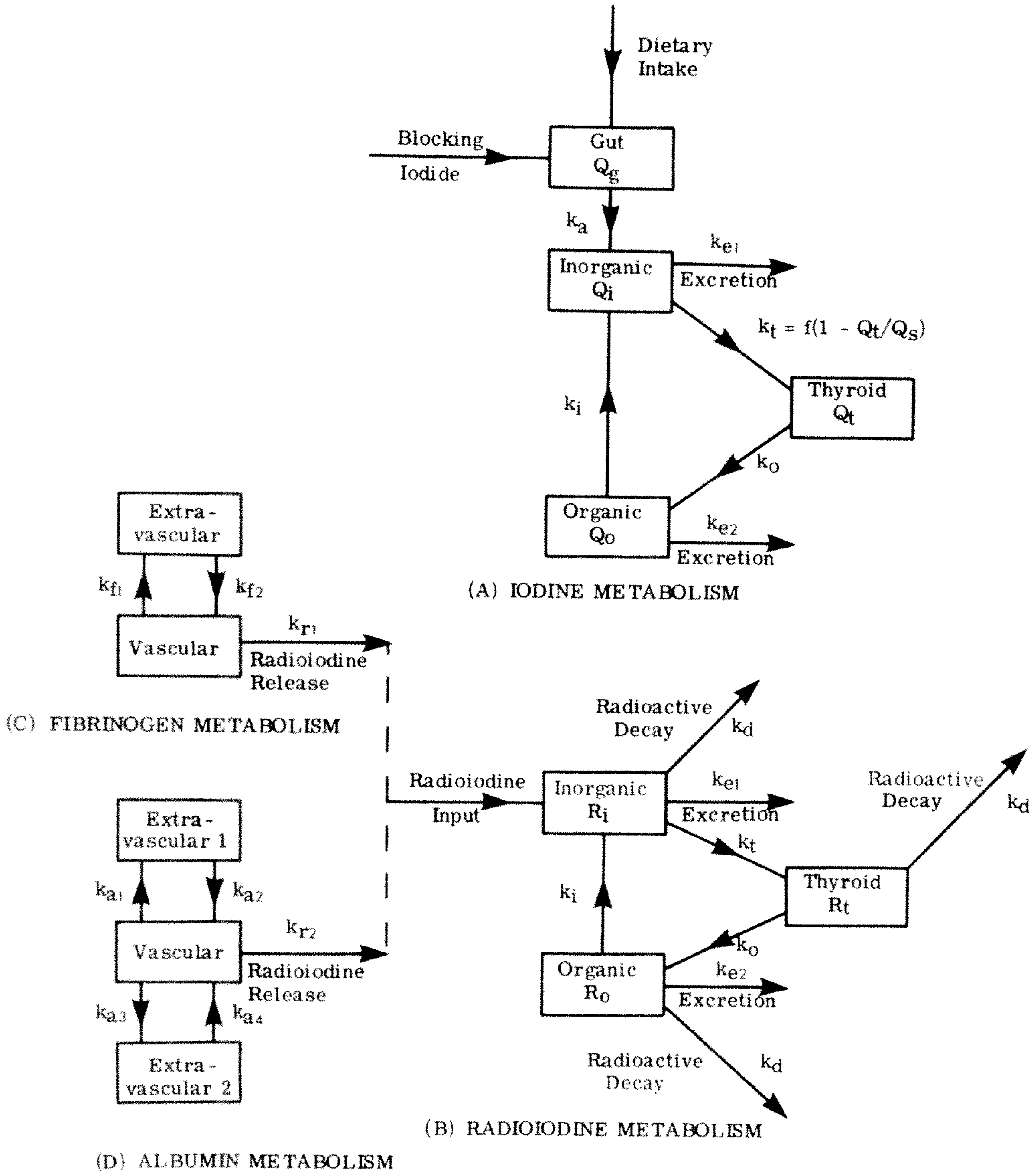
In the case of injected ^{125}I- or ^{131}I-iodide, substantial thyroid protection may theoretically be achieved by a single oral dose of inorganic iodide, for example a 90% reduction in radiation dose is produced by only 20 mg iodide. Repeating the initial blocking dose is of little value.

A single blocking dose, however, affords poor protection against radioiodine released from labelled plasma proteins. Both for short-lived proteins such as fibrinogen, and for the longer-lived proteins such as albumin, the optimum dosage schedule appears to be stable iodide given daily for two to three weeks. For instance, 10 mg daily for a fortnight will reduce thyroid irradiation by a factor of ten following injection of ^{125}I-fibrinogen.

During investigations in which radioiodine-labelled pharmaceuticals are injected into human subjects it is a conventional radiation protection measure to inhibit or "block" the thyroid uptake of radioiodine released by catabolism of the pharmaceutical in order to minimize radiation dose to the gland; indeed for many years it was the practice of the M.R.C. Isotope Advisory Panel to authorize the use of such pharmaceuticals subject to the proviso that the thyroid gland be blocked (Ellis *et al.*, 1977). Blocking is usually achieved by oral administration of inorganic iodide, a fraction of which is subsequently taken up by the thyroid gland, militating against further uptake as the gland content approaches saturation. However, the procedures to be followed to ensure satisfactory thyroid blocking have not been formally stated and the question of iodide dosage has been left as a matter for the individual clinician, with the result that while some investigators administer only a few milligrams of potassium iodide daily, others prefer to give several hundred milligrams of iodide for several weeks. Such variations are probably unimportant in the biochemically-normal subject, but it has recently been suggested that in the geriatric or coronary patient the hazard associated with the administration of iodide for thyroid blocking may be greater than the radiation hazard resulting from the absence of any blocking agent at all (Denham and Himsworth, 1974). It therefore seems desirable to minimize, so far as possible, the mass of iodide employed for thyroid blocking, at least in these cases, and this paper reports our investigations into the efficacy of various thyroid blocking regimes.

METHOD

The present study takes as its basis the compartmental model of iodine metabolism used by Ramsden *et al.* (1967), an accepted simplification of a complex physiological situation (Colard *et al.*, 1965; Adams and Bonnell, 1962; Stanbury *et al.*, 1954; Riggs, 1952). This model employs three interactive iodine "pools" that suffice to describe the observed kinetics of iodine metabolism in man, but it does not include an explicit description of iodine absorption from the gut. Since the latter is the usual route of administration of blocking iodide and since any delay associated with absorption could have significant effect, a further pool has been added to the model to simulate gastrointestinal absorption of iodide (Fig. 1A). Absorption is rapid and is assumed to take place with a rate constant of 5%/min (Keating and Albert, 1949). One of the functional pools of the model represents iodine contained in the thyroid and the phenomenon of thyroid blocking is modelled by the non-linear uptake of inorganic blood iodide into that pool: the rate constant, k_t, progressively reducing the uptake of iodide as the thyroidal iodine content, Q_t, approaches saturation. In the absence of further blocking doses the iodine content of the thyroid slowly falls to its normal equilibrium value as metabolism proceeds. The work of Riggs (1952) and others has established the magnitudes of the above rate constants (Table I), so that the model may be written as a set of four simultaneous differential equations with no unspecified parameters.



(A) IODINE METABOLISM

(C) FIBRINOGEN METABOLISM

(B) RADIOIODINE METABOLISM

(D) ALBUMIN METABOLISM

FIG. 1.

Compartmental schemes used to model the kinetics of iodine and radioiodine in man. Section A represents the kinetics of inactive iodine and Section B the kinetics of radioiodine. Sources of radioiodine, from the catabolism of labelled plasma proteins, are shown in sections (C) and (D). Numerical values for the model are given in Table I.

TABLE I

NUMERICAL VALUES USED IN THE MODEL

A. *Iodine kinetics*

Dietary intake 240 μg/day[1]

Rate constants

$k_a = 3.0/\text{hr}$[2]

$k_{e1} = 1.92/\text{day}$[1]

$k_o = 0.0096/\text{day}$[1]

$k_i = 0.048/\text{day}$[1]

$k_{e2} = 0.00048/\text{day}$[1]

Thyroid uptake rate

$k_t = f(1 - Q_t/Q_s)$ where $f = 0.97/\text{hr}$ and $Q_s = 8.35$ mg[1]

Steady state values

$Q_g = 0.003$ mg

$Q_i = 0.125$ mg

$Q_o = 1.610$ mg

$Q_t = 8.125$ mg

B. *Radioiodine kinetics*

$k_d = 0.0116/\text{day}$ (^{125}I)

$= 0.0860/\text{day}$ (^{131}I)

C. *Fibrinogen kinetics*

$k_{f1} = 0.576/\text{day}$[3]

$k_{f2} = 3.05/\text{day}$[3]

$k_{r1} = 0.24/\text{day}$[3]

D. *Albumin kinetics*

$k_{a1} = 1.09/\text{day}$[4]

$k_{a2} = 8.20/\text{day}$[4]

$k_{a3} = 0.44/\text{day}$[4]

$k_{a4} = 0.48/\text{day}$[4]

$k_{r2} = 0.108/\text{day}$[4]

References:
[1] Ramsden *et al.*, 1967.
[2] Keating and Albert, 1949.
[3] Takeda, 1966.
[4] Dykes, 1968.

To express the kinetics of radioactive iodine in the system, a similar compartmental scheme is required (Fig. 1B) in which the contents of each pool are subject to radioactive decay at the appropriate rate, k_d. However, no gastrointestinal pool of radioiodine is necessary since only its intravenous administration has been simulated. Additional pools have been added to model the release of radioiodine into the blood following breakdown of a labelled protein: in the particular cases of fibrinogen and albumin which we have considered, the two compartment model of Takeda (1966) (Fig. 1C) and the three compartment model of Dykes (1968) (Fig. 1D) respectively were adopted. Finally, thyroid uptake of radioiodine is essentially independent of thyroid radioiodine content, R_t, and is controlled by the rate constant, k_t, determined by the thyroid content of inactive iodine, Q_t.

Evaluation of the efficacy of various blocking dose regimes requires the determination of the corresponding integral with respect to time of thyroid radioactivity from the time of injection until radioactive decay is complete. Each determination therefore implies the complete solution of between seven and ten simultaneous differential equations containing non-linear terms. Faced with this task we abandoned mathematical analysis in favour of a computer method using established techniques of numerical analysis to solve the differential equations. This was incorporated into an interactive computer-graphic simulation of the model, written in Fortran and run on a Honeywell DDP516 computer. A broad spectrum of run-time options was programmed allowing, for example, interactive nomination of a wide range of blocking dose regimes and specification of the manner in which radioiodine was released into the blood pool. Other options provided control of the graphic presentation and computer-file records of the system variables generated during ensuing simulation runs. Since these simulations were costly of computer time, special purpose batch-mode programs were produced from the interactive program which were run on a Hewlett Packard 3000 computer, to provide tables of thyroid radioactivity corresponding to various clinical situations.

After each simulation run, absorbed radiation dose to the thyroid was calculated as the product of the above time integral and the dose-rate from the appropriate radioisotope of iodine. The dose-rate to the thyroid was calculated by the simplified methods of Emery and Fowler (1971) assuming a uniform distribution of radioiodine in a gland of mass 20 g. The contribution from radioiodine in the rest of the body was assumed negligible by comparison.

Using the above method, absorbed radiation doses to the thyroid were calculated for a number of blocking dose regimes administered as protection against the two commonly-used radioisotopes of iodine, ^{125}I and ^{131}I. These isotopes were assumed to have been injected either unbound as iodide, as iodine-labelled fibrinogen or as iodine-labelled albumin.

RESULTS

Radiation doses to the thyroid following administration of the chosen radiopharmaceuticals were calculated first, assuming no blocking with inactive carrier iodide (Table II). The reduction in thyroid irradiation which can be achieved by oral administration of inorganic iodide simultaneously with the radio-pharmaceutical is shown in Fig. 2. Since the timing of this blocking dose is a major factor in the efficacy of blocking, a series of computer runs was made to determine the nature of the effect. Results for ^{125}I- and ^{131}I- iodide are shown in Fig. 3 in

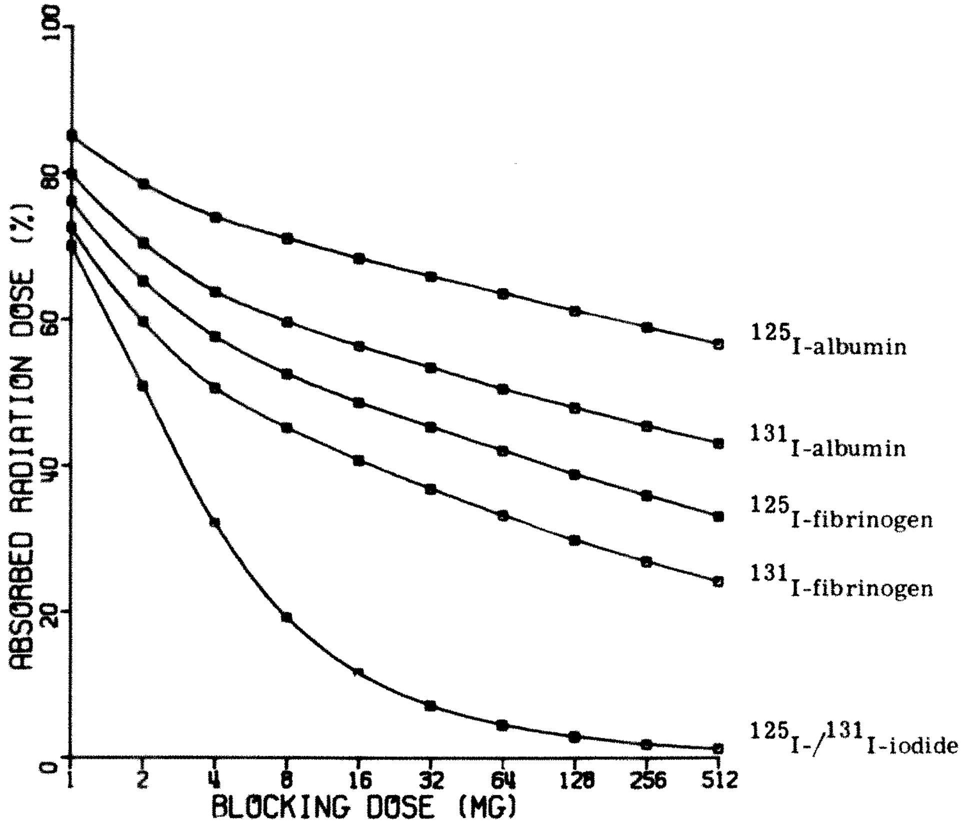


Fig. 2.

Effect of blocking on thyroid radiation dose. Absorbed radiation dose is given as a fraction of that incurred in the unblocked case.

TABLE II

Unblocked thyroid radiation dose

Radiopharmaceutical	Thyroid radiation dose (rad/μCi injected)
^{125}I-iodide	0.99
^{131}I-iodide	1.30
^{125}I-fibrinogen	0.94
^{131}I-fibrinogen	0.92
^{125}I-albumin	0.90
^{131}I-albumin	0.51

which the method of presentation adopted generates a three-dimensional surface whose shape for radioiodide contrasts sharply with those for the radioiodinated proteins. For example, Fig. 4 shows the analogous surface for administration of ^{125}I-fibrinogen; it is typical of those for the other proteins examined, although, as might be expected from Fig. 2, the surfaces for similar activities of different radiopharmaceuticals stand at different heights.

Another aspect of thyroid blocking for which detailed results have been obtained concerns the effects of dividing a given mass of inorganic iodide into various equal blocking doses. The first is administered simultaneously with the radioactive agent and the remainder at fixed intervals thereafter. Where such blocking doses are used to protect the thyroid against radioactive iodide, protection is in all cases diminished compared with the same mass of blocking iodide given in one dose. However, in the case of labelled-fibrinogen and labelled-albumin, a dramatic improvement in protection is obtained. This is illustrated in Fig. 5, which shows the effect of dividing in various ways 128 mg of iodide used in protection against ^{125}I-fibrinogen. Similarly shaped surfaces at different heights were obtained for other blocking doses and comparable results were obtained for both radioisotopes and labelled proteins. Too many data have been collected for presentation here but copies may be obtained from the authors.

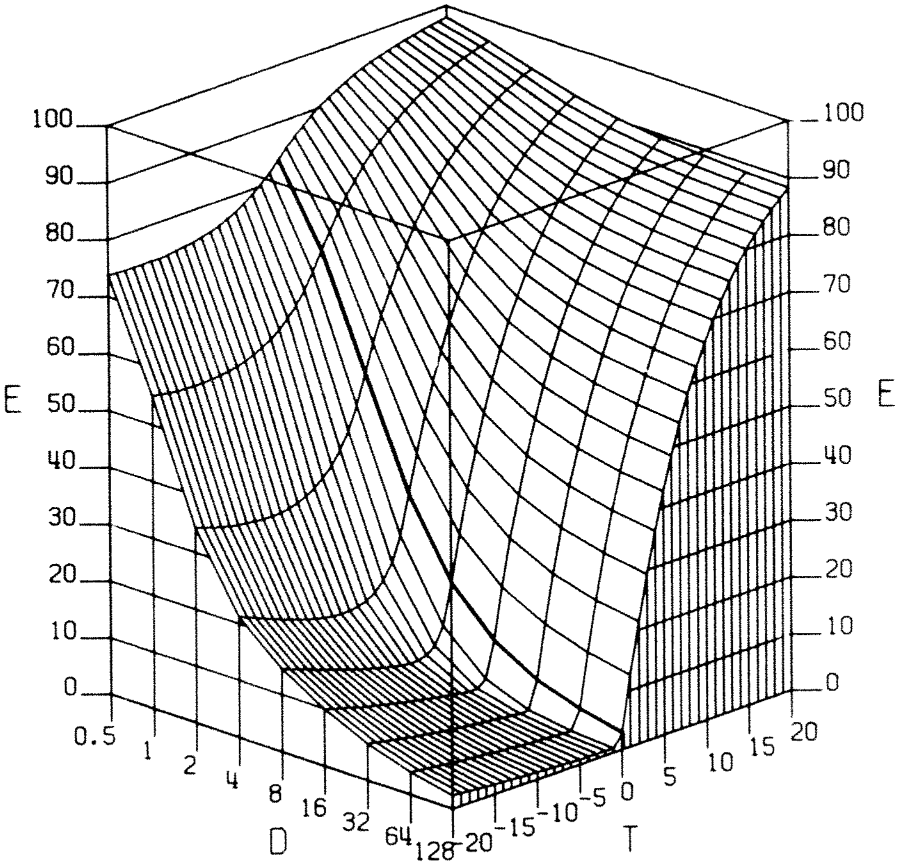


FIG. 3.

Computer projection of the surface describing thyroid radiation dose as a function of blocking dose and time administered. Absorbed radiation dose (E : y-axis) is expressed as a fraction of the dose incurred in the unblocked case. Units of blocking dose (D : z-axis) are mg iodide. Time of blocking (T : x-axis) is in hours before (negative values) or after (positive values) injection of the radioiodide.

DISCUSSION

Radioiodide

When no blocking agent is administered, the model predicts an absorbed radiation dose to the thyroid of 1.3 rad/μCi of ^{131}I injected and 0.99 rad/μCi of ^{125}I injected. These results accord with the calculations made by the International Commission on Radiological Protection and by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine (U.S.A) which for ^{131}I range from 1.2 to 2.1 rad/μCi and for ^{125}I from 0.79 to 1.2 rad/μCi injected (I.C.R.P., 1971; M.I.R.D., 1975).

In the case of radiation protection against radioiodide, substantial thyroid protection is conferred by a single dose of inactive iodide (Fig. 2). For instance, the thyroid radiation dose relative to the unblocked case can be reduced by an order of magnitude for both ^{125}I and ^{131}I using 20 mg of oral iodide. Using 32 mg, the absolute radiation doses to the thyroid are 0.071 rad/μCi of ^{125}I and 0.094 rad/μCi ^{131}I. Any further reduction is progressively more expensive in terms of the mass of blocking iodide required; neither is any advantage obtained by subdividing the blocking dose, so that 20 mg may represent a good compromise between radiation risk and biochemical hazard. From Fig. 3 it can also be seen that the optimum time of administration of this 20 mg dose is about one hour before the exposure to radioiodine and that any delay in blocking incurs a progressively increasing penalty.

Radioiodine-labelled proteins

Radiation protection against radioiodinated proteins presents a distinct contrast because the radioiodine is released for days or weeks, and over such periods normal iodine metabolism reduces the iodine content of the thyroid and hence the blocking effect. Despite the differences in biological half-life between the proteins that we have considered and despite the differences in physical half-life between their radioactive labels, the surfaces generated in the presentation of Figs. 4 and 5 are closely similar in all cases. As might be expected, a single oral blocking dose of iodide confers very little thyroid protection following the injection of a radioiodinated protein and considerably better protection can be produced by administering the same mass of blocking iodide over an extended period. This is illustrated in Fig. 5 which shows the effect of giving a total of 128 mg of iodide in seven different dosage schedules. At an interval between blocking doses of one hour a steady reduction in thyroid radiation dose is obtained as the iodide is divided more and more. On the other hand, at an interval of 256 hours, less protection is afforded by dividing the dose. For any given number of multiple doses there exists an optimum interval between them which produces the characteristic valley in the surface of Fig. 5. Calculation shows that the location of this valley corresponds to thyroid blocking therapy which extends over a more or less constant period of two or three weeks. For protection against ^{125}I-fibrinogen, for instance, 128 mg of iodide administered in this way reduces the thyroid radiation dose to 0.07 rad/μCi, that is by a factor of 14 relative to the unblocked case or by a factor of five relative to the case of a single 128 mg blocking dose (0.37 rad/μCi).

Risk factors

In the absence of quantitative information relating the risk of induction of hyperthyroidism to the administration of iodide it seems reasonable to assume that the risk is related to iodine concentration at some real but unidentified site in the body. If iodine turnover at this site obeys first order kinetics, then there is a limited number of possible relationships between the administered blocking dose and peak concentration or highest risk. In general terms,

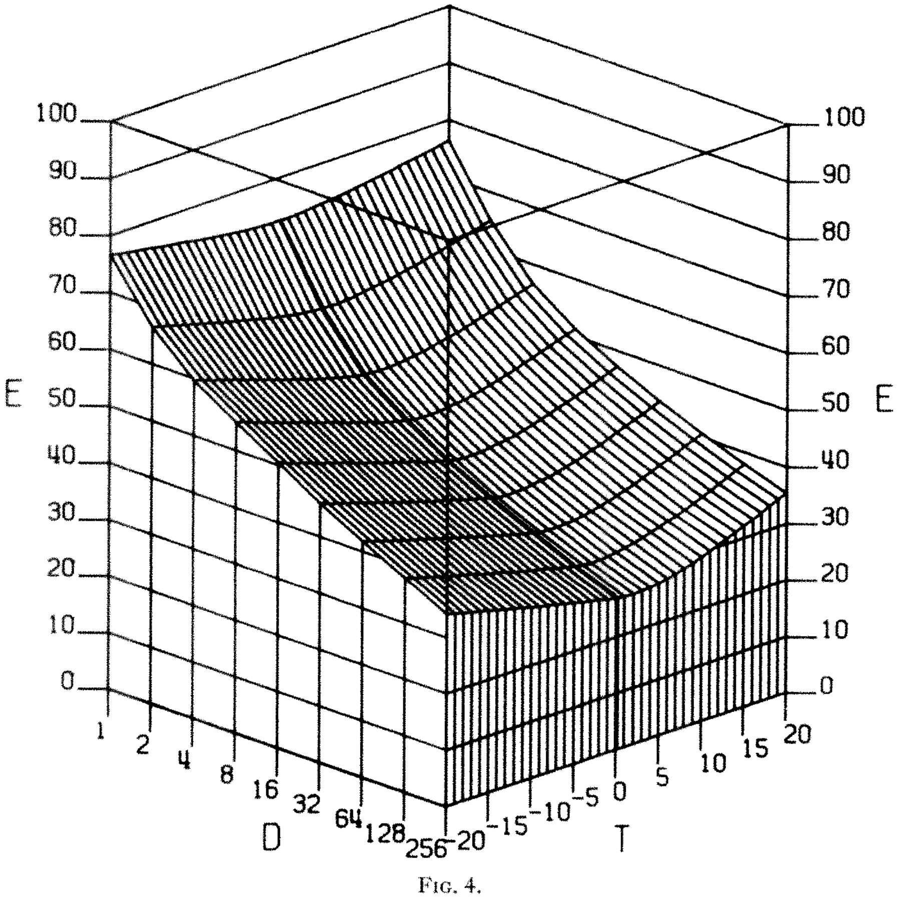


Fig. 4.

Computer projection of the surface describing thyroid radiation dose after the injection of ^{125}I-fibrinogen as a function of blocking dose and time administered. Axes as for Fig. 3.

if the iodine turnover at this sensitive site is slow, peak concentrations will tend to be proportional to the total mass of iodide administered, whereas if turnover is fast, peak concentrations will tend to be proportional to the mass of each individual dose. Although in the former case subdividing the blocking dose would have little effect upon the risk of inducing hyperthyroidism, in the latter it might substantially reduce the risk.

While the above reasoning favours dose-splitting as a means of reducing the risks associated with thyroid blocking, quantitative recommendations cannot be made since, as is so often the case in clinical work, one is balancing two risks of uncertain magnitude. Thus one is concerned to take reasonable steps to reduce the thyroid radiation dose resulting from the use of radioiodine-labelled pharmaceuticals, but one is also anxious to minimize the mass of inorganic iodide employed. A reasonable compromise is to reduce the thyroid radiation dose by a factor ten, any further significant improvement only being possible with a substantial increase in the total mass of iodide administered. This finding is not of course relevant to thyroid blocking for technical reasons, for instance during protein turnover studies, in which complete recovery of metabolized radioiodine from the urine is desired.

CONCLUSION

Whichever total mass of iodide the individual clinician decides to employ for thyroid blocking, two recommendations can be made: the first is that for protection against radiopharmaceuticals such as labelled fats, denatured proteins etc, where the label is rapidly split off by metabolic processes, or for protection against unbound ^{125}I or ^{131}I, a single oral blocking dose of inorganic iodide is adequate if given either at the time of injection or preferably an

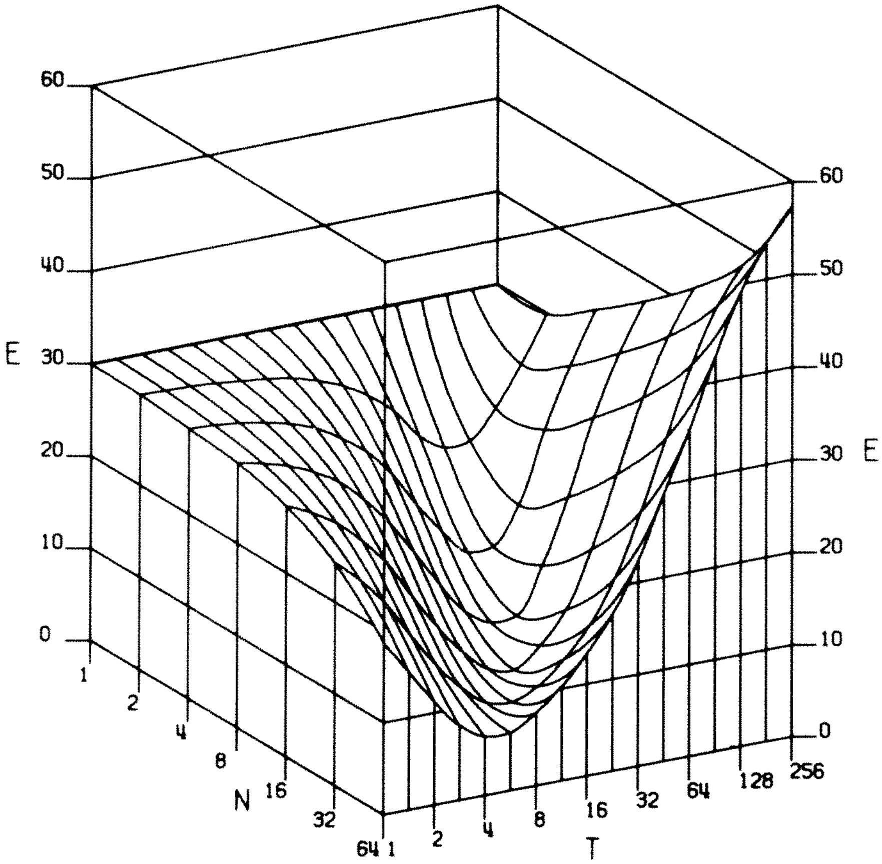


FIG. 5.

Computer projection of the surface describing thyroid radiation dose following the administration of 128 mg iodide divided into various numbers (N : z-axis) of equal blocking doses given at various time intervals (T : x-axis) in hours, starting with the injection of ^{125}I-fibrinogen.

hour before. The second is that for protection against ^{125}I- or ^{131}I-labelled fibrinogen or albumin a single blocking dose is not adequate. The iodide should be divided into daily doses to be given for two to three weeks from the injection of the protein. These recommendations are embodied in a recently-published report (Ellis *et al.*, 1977) of the M.R.C. Isotope Advisory Panel.

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Book reviews

Tomography: Physical Principles and Clinical Applications. By J. T. Littleton. Section 17: Golden's Diagnostic Radiology. pp. xiii + 841, illus., 1976 (Baltimore; Williams and Wilkins Co.), $57.50.

Tomography has been something of a Cinderella in the British and American radiological literature. This book goes some way towards providing Cinderella with slippers for the ball. It is a large book, 863 pages of text costing $57.50—roughly 4.1 pence per page. This puts it beyond the price which individual British radiologists can afford, granted the "clobbering of the rich" promised by Mr. Healey some years ago, and the short-sighted, peculiarly British, system of personal taxation and allowances for full-time professional workers. With the present and ever-continuing squeeze on University and National Service budgets, radiologists have to be extremely selective about the books they recommend for purchase by their departmental or university libraries. All publishers in the English language please note.

This book is clearly a labour of love, and as such is to be recommended. But it is curiously patchy. The reviewer, with a special interest in the pituitary, finds his interest dismissed in two very inadequate pages. He is instead referred to two chapters in an even more expensive set of books.

This book confirms the view that tomography is still more of an art than a science. Some parts are excellent. Buy it if you can. The second edition could be much better than the first; the first had to be written.

F. H. DOYLE.

Graphs and Tables for use in Radiology. By F. Wachsmann and G. Drexler, pp.240, 1976 (Springer Verlag) DM48.00.

A most comprehensive reference book but difficult to use. It is a unique assemblage of quantitative data taken from ICRU, ICRP, DIN, and many authoritative listed references. The information is condensed into 240 pages in four languages (English, German, French and Spanish). Each graph is labelled in four languages and a similar choice is given at the head of each row and column of each table of data. The book borders on complete confusion but survives. I hazard that the addition of a further language would have led to chaos! The eye frequently skates from the English phrases to the other language options and back again with linguistic edification which can confuse the original purpose. Luckily English occupies the first word, sentence, paragraph or page as the case may be.

However, this second enlarged edition (of a book first published in 1957) contains a wealth of information. Radiotherapy dose data are comprehensively summarized to 100 MV for X-radiation and for accelerated particles. Properties of primary X-radiation beams are well documented. There are useful sections on dosimetry, nuclear medicine and radium therapy, and a brief section on diagnostic radiology. Sections on general biology, radiation biology and radiation protection make interesting reading. This is a useful reference text with a linguistic challenge.

B. L. REECE.

1978, *British Journal of Radiology*, *51*, 273–280 APRIL 1978

Display of cross sectional anatomy by nuclear magnetic resonance imaging

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ABSTRACT

High definition cross-sectional images produced by a new nuclear magnetic resonance (NMR) technique are shown. The images are a series of thin section scans in the coronal plane of the head of a rabbit. The NMR images are derived from the distribution of the density of mobile hydrogen atoms. Various tissue types can be distinguished and a clear registration of gross anatomy is demonstrated. No known hazards are associated with the technique.

The first images produced by nuclear magnetic resonance (NMR) techniques consisted of two spots corresponding to a thick cross-section through two tubes of water (Lauterbur, 1973). In the past few years, the quality of images has improved as new equipment and methods have been developed (Lauterbur, 1974; Hinshaw, 1974, 1976; Garroway *et al.*, 1974; Kumar *et al.*, 1975; Mansfield and Maudsley, 1977a, b). The early NMR images were produced on modified NMR spectrometers and consequently the size of the sample was limited to the order of 1 cm. There is growing interest in applying the techniques to humans and, in fact, several laboratories are designing and building equipment for that purpose. We have recently built an intermediate sized system designed to investigate the medical feasability and usefulness of NMR imaging by studying small aminals (Andrew *et al.*, 1977).

This paper presents a series of thin-section NMR images taken through the head and forelegs of a rabbit and shows the close correspondence between the NMR images and the anatomical sections. The images represent the distribution of mobile hydrogen atoms although other NMR properties could have been used as the basis of the images. *In vivo* images of the human hand, which can also be investigated by this intermediate system, have been produced and have been published elsewhere (Hinshaw *et al.*, 1977).

It is too early to predict how NMR imaging will stand alongside other techniques for the display of anatomical structure. NMR, like computerized axial tomography, produces a cross-sectional image of the object being scanned with good discrimination of soft tissues. Unlike computerized transverse axial scanning, however, NMR is not limited to the transverse plane; any plane in any orientation can be chosen. NMR is a very powerful and well-established method of studying the properties of materials at the molecular level. It is to be anticipated therefore that NMR techniques may provide functional information of diagnostic value in addition to displaying anatomical structure.

PRINCIPLES

It is beyond the scope of this paper to present more than a brief discussion of NMR with a view towards explaining how the images are produced and what properties of the sample are actually being observed. Atomic nuclei which have a magnetic moment respond to radio-frequency electromagnetic radiation when placed in a magnetic field. The response is sharply resonant at a frequency, ω, which is directly proportional to the strength of the magnetic field. This can be written $\omega = \gamma B$ where the constant of proportionality, γ, is called the gyromagnetic ratio. The gyromagnetic ratio is different for each element and, as a consequence, the signal from the nuclei of a selected element can be observed without interference from any other. In the experiments reported here, we observed the resonance signal of protons, the nuclei of hydrogen, which have a gyromagnetic ratio of 42.6 MHz/tesla. Other nuclei with magnetic moments which occur in living systems such as ^{13}C, ^{14}N, ^{17}O, ^{23}Na, ^{31}P and ^{43}Ca, give NMR signals which are one or more orders of magnitude weaker than that of protons, due either to low natural abundance or inherantly weak resonance behaviour.

The importance of NMR as an analytical technique results from the fact that the NMR signal contains detailed information at the molecular level.

For the nuclei of a given element, the resonance signal from each nucleus in a given molecule occurs at a slightly different frequency. These frequency differences relative to a standard are known as chemical shifts and depend on the molecular environment of the nucleus. The chemical shift spectrum differs for each chemical compound thus enabling chemical analysis to be made from the signal.

The particular NMR properties most relevant to this work are the T_1 and T_2 relaxation times which are of interest because of their influence upon the strength of the NMR signal. The relaxation time T_1 is the characteristic time required for the nuclear magnetic moments to regain thermal equilibrium with their environment and is a measure of molecular motion. The value of T_1 decreases as the amount of motion which has spectral components near the resonance frequency increases. The relaxation time T_2 is the characteristic time required for the nuclear magnetic moments of a given spectral line to regain thermal equilibrium with each other and is related to the molecular motion. The value of T_2 tends to increase with increased motion. For solids, particularly at low temperatures when there is little thermal motion, T_2 is often very short while T_1 is long. In simple liquids, however, there is considerable thermal motion which causes T_1 and T_2 to be equal. Thus, with some justification, one can think of those samples with the ratio T_2/T_1 near unity as "liquid-like" and those with the ratio much less than unity as "solid-like". The T_1 and T_2 values of tap water, for example, are typically three seconds but when the water is frozen T_1 lengthens to minutes and T_2 shortens to tens of microseconds.

In addition to information at the molecular level, the NMR signal can also provide macroscopic spatial information. Since the resonance frequency is proportional to the strength of the magnetic field, if the field is not constant over the sample but has a uniform gradient in one direction, then the inherently narrow resonance is broadened in a way that depends upon the shape of the sample. To be specific, if the field B can be written $B=B_0+gy$ where g is the gradient strength in the y direction, then the resonance spectrum, $f(\omega)$, is proportional to the projection of the sample onto a line in the y direction. In other words, an element of sample at a point (x, y, z) has a resonant frequency $\omega=\gamma(B_0+gy)$ and thus adds its signal to the spectrum at that frequency. The fact that the spectrum corresponds to a projection of the sample when a magnetic field gradient is applied has been known for a long time (Gabillard, 1951). Recently this fact has been used to form two-dimensional images by recording the spectra for many different gradient directions and then reconstructing the image from the spectra, or projections, with a computer algorithm similar to that employed by the CAT X-ray scanners (Lauterbur, 1973).

The technique used to produce the images presented in this work differs from the more traditional reconstruction from projections. In this work a further experimental method is used in which the NMR signal from selected regions of the sample is accepted while that from other regions is rejected. This technique, which is explained in detail elsewhere (Hinshaw, 1976), is based on the fact that a time-dependent field gradient applied to the sample makes the magnetic field in the sample time-dependent everywhere except in one plane which is normal to the direction of the gradient. Thus the NMR signal from everywhere except that one plane is also time-dependent and can be removed by careful signal processing, leaving only the signal from the selected plane, or "sensitive plane". An NMR saturation phenomenon is also involved in this selection process but its discussion is not necessary here. If two orthogonal time-dependent gradients are applied, for example in the x and z directions, the result is a "sensitive line" in the y direction. If three orthogonal time-dependent gradients are applied the result is a "sensitive point" at the intersection of the three sensitive planes.

METHOD

The images shown in this paper were made by applying both time-dependent and static magnetic field gradients. The geometry used is shown in Fig. 1. Time-dependent gradients were applied in the x and z directions producing a sensitive line through the sample in the y, or vertical, direction. A static field gradient was applied in the y direction along the sensitive line. With this arrangement of gradients, the observed NMR signal was produced by the sample in the selected sensitive line and the spectrum corresponded to the distribution of material along the sensitive line. The spectrum was stored in a computer memory and displayed as a line on an oscilloscope screen with the beam intensity corresponding to the spectrum amplitude. Thus a dense region of the sample somewhere along the sensitive line would produce a corresponding peak in the spectrum and finally a bright spot on the oscilloscope screen. The complete image was formed by scanning the sensitive line through the sample and simultaneously moving the display line across the oscilloscope screen. In order to form separate

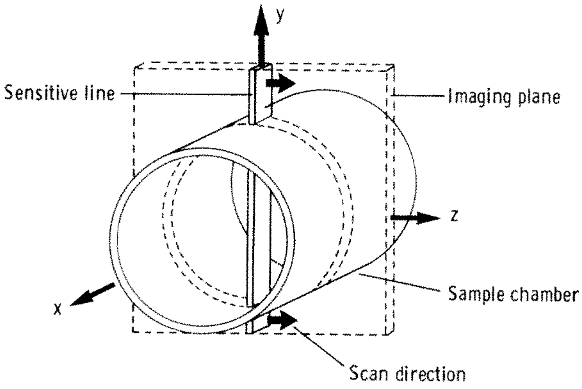

FIG. 1.

Diagram of the sample chamber geometry. The sensitive line scans slowly from left to right through the sample chamber during the formation of an image. The sample chamber is 8 cm in diameter, the imaging plane is ~3 mm thick, and the sensitive line is ~0.4 mm wide. The sample chamber is mounted between the pole faces of a magnet which applies a magnetic field in the z direction.

images of successive planes, the sample was moved along the axis of the sample chamber.

The uniform magnetic field of 0.7 tesla was provided by a Varian iron-core electromagnet with 30 cm diameter pole faces and a 13 cm gap. The sample chamber was an 8 cm diameter glass tube mounted between the magnet pole faces. The coils producing the three orthogonal gradients were mounted on the pole faces. The strength of the three gradients was of the order of 10^{-4} tesla/cm. The x and z gradients had a sinusoidal time dependence with a frequency of 6Hz. The cross-sectional shape of the sensitive line was determined by the strength of these two gradients and was roughly 3 mm in the x direction and 0.4 mm in the z direction. The static y gradient was adjusted to resolve 128 independent points at 0.4 mm intervals in the vertical, or y, direction. The position of the sensitive line was stepped horizontally 0.4 mm for each line, giving a final image consisting of 128 by 128 independent picture points. The rate of scan was such that the image was completed in about 15 min.

The resonance phenomenon was excited and observed by a purpose-built 30 MHz NMR spectrometer operating in the pulse Fourier transform mode. Details of the spectrometer and its operation will be discussed elsewhere.

The image data were stored on cassette tape which enabled interactive computer image processing to be done at a later time. The images were photographed from the screen of the display oscilloscope with a 35 mm camera. Dense regions of mobile protons produced bright areas on the display and thus white areas on the prints made from the 35 mm film. The images were actually displayed as a 256 × 256 array of dots rather than 128 × 128 in order to reduce the dot size and produce a smoother image.

Other modes of data display are possible with the existing equipment, including a list of the actual numbers corresponding to each picture element. Colour images can be obtained from the monochrome oscilloscope by decoding the image data into three primary components which are consecutively displayed and photographed through colour filters (Holland and Bottomley, 1977). A computer driven photo-scanner has recently been developed which exposes photographic print paper point-by-point to build up either monochrome or full colour pictures (Bottomley *et al.*, 1978). With these methods of display, the colour and intensity of an image can be used separately to represent two independent NMR parameters such as density of mobile protons and T_1 relaxation time.

RESULTS

The head and fore-limbs of a freshly killed rabbit were introduced into the sample chamber. A series of scans in the coronal plane were made at successive 5 mm intervals along the length of the head. At the conclusion of the experiment the rabbit was embedded in Plaster of Paris and after deep freezing overnight serial coronal sections were made with a band saw at 1 cm intervals along the length of its head. The sections were photographed on each side and also X-rayed using both a screen and a non-screen technique for optimum display of bone and soft tissues. It is not possible to ascribe an exact registration between the NMR images and the anatomical sections since the precise location of the former was not defined; nevertheless, a close correspondence was immediately evident when the two series were placed side by side.

The strongest signals, which appear as white in the images, are associated with bone marrow as in the diploic space of the frontal bones, with fat-containing connective tissue as within the extra-ocular muscle cone, and with certain mucous membranes such as that lining the palate. Cortical bone and teeth give a very low signal and, like air-filled cavities, appear black in the image. Muscle and nervous tissue give signals of intermediate strength and appear in shades of grey.

Figure 2A is an NMR image taken through the middle of the orbits. The corresponding anatomical section is shown in Fig. 2B, and Fig. 2C is an annotated diagram indicating the recognizable structures. The section includes part of the anterior cranial cavity which is formed by the pre-sphenoid bone inferiorly and the frontal bones dorso-laterally. The cortical component of this bony ring is seen as a thin black line with the short lateral extension of the frontal bones to form the supra-orbital ridges clearly defined. The marrow within the diploic space of the frontal bones and the medullary cavity of the sphenoid appears white in the image.

In the rabbit the shallow orbital cavity becomes confluent below with the temporal fossa and there is no bony optic capsule apart from the supra-orbital ridges. The globes are defined by an outer thin black ring representing the fibrous sclerotic coat and within each the lens shows as a dark ellipse. It is just possible to discern the outline of the extra-ocular muscles and in Fig. 3C fat within the muscle cone produces a triangular white area in the image, reflecting a very high NMR signal. This cone of tissue tapers towards the orbital apex where it is seen to surround a short segment of optic nerve. Between the orbits are the posterior ethmoid air cells and below them is the nasal cavity which appears as a dark ellipse on account of the air within it. A horizontal white band representing the soft palate forms its inferior boundary and separates it from the buccal cavity. Immediately below each orbit a portion of the maxilla is included in the section together with an adjacent segment of the horizontal ramus of the mandible. The cortical bone and teeth are registered in black and where marrow occurs within the section this is represented in white. The changing contribution of cortical bone and marrow accounts for the different appearance of these bones in the three adjacent orbital sections shown in Fig. 3A, B

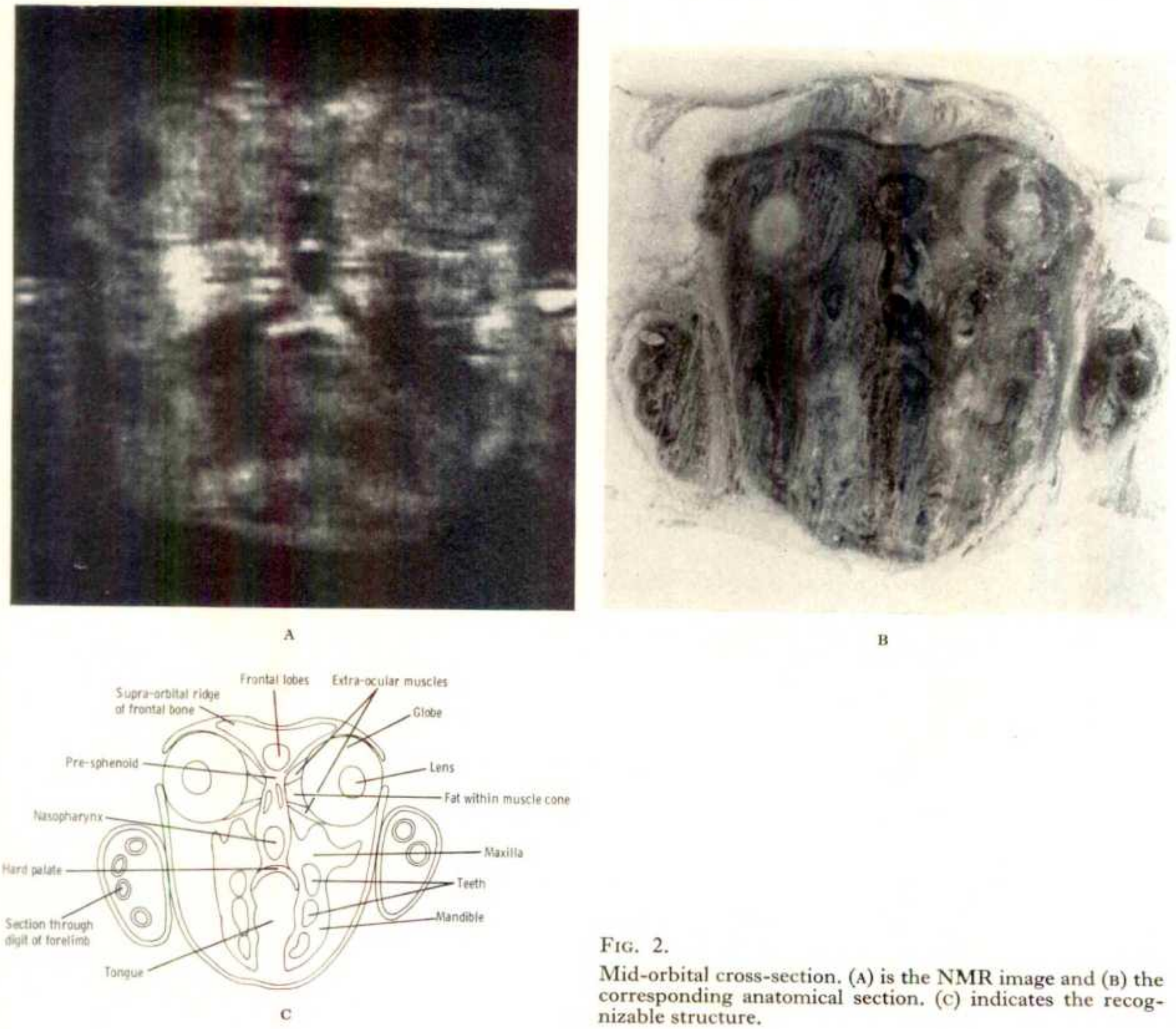

FIG. 2.

Mid-orbital cross-section. (A) is the NMR image and (B) the corresponding anatomical section. (C) indicates the recognizable structure.

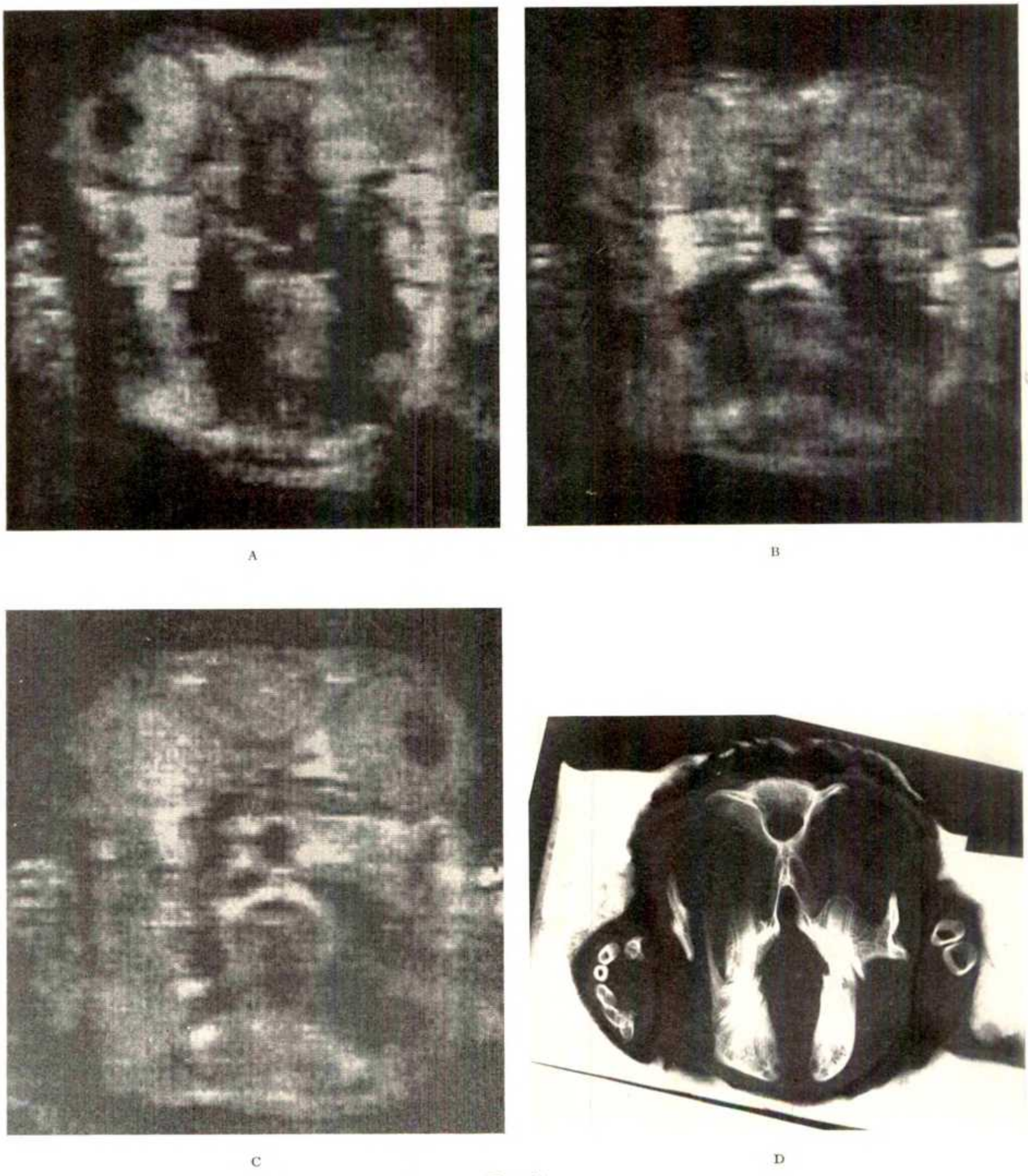

FIG. 3.

(A), (B) and (C) are NMR scans of three adjacent orbital sections. (D) is a radiograph of the anatomical section corresponding to (B). The white region surrounding the section is the Plaster of Paris in which the rabbit was embedded.

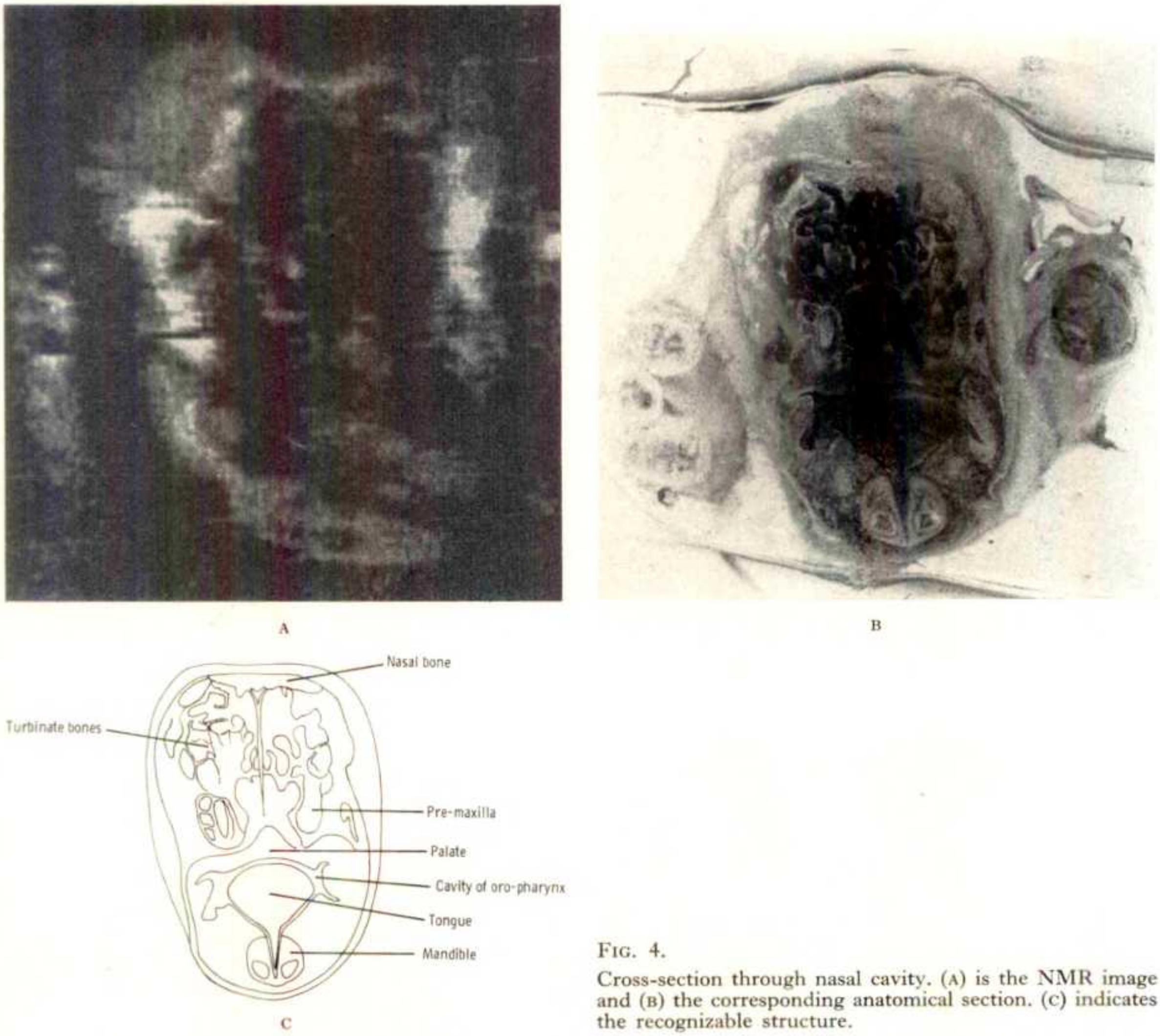

Fig. 4.

Cross-section through nasal cavity. (A) is the NMR image and (B) the corresponding anatomical section. (C) indicates the recognizable structure.

and C. The tongue, which is made up of muscle, is seen as a greyish granular structure between the mandibular rami in apposition with the soft palate above. A radiograph of the mid-orbital section is shown for comparison in Fig. 3D.

The shape of the skull in the rabbit is much influenced by the large nasal passages. Their roof is formed by the nasal bones; the side walls by the maxillae and pre-maxillae and the floor partly by medial palatine processes of these bones being completed posteriorly by the palatine bones. Within the nasal cavity is an extensive mucous membrane supported by thin bony plates, the turbinals or scroll bones, which are attached to the maxillae, nasal and ethmoid bones. These are clearly seen within the air-filled nasal cavity in Fig. 4A which is an NMR section taken through the anterior part of the nasal cavity. The corresponding anatomical section is shown in Fig. 4B and an annotated diagram, Fig. 4C, indicates the structures identifiable within the section.

Discussion

In the NMR images of the rabbit, white corresponds to a dense region of mobile protons and black to an absence of mobile protons. It is perhaps worth looking at this correspondence more closely. Experimentally, the image represents the distribution of NMR signal strength. Based on a rather simple theoretical model, we can say that three properties of the sample determine the NMR signal strength. The most obvious property is simply the number of relevant nuclei in the region being observed; in our case the number of protons, or hydrogen atoms. The other two properties are the T_1 and T_2 relaxation times. Due to the details of the NMR technique used to obtain the spectra, any protons in the sample either with T_2 less than about 1 ms or T_1 longer than a few seconds will not be observed. These requirements eliminate the protons in solid-like material. The remaining protons are observed with a signal strength, or intensity, which is proportional to the density of observable protons. The intensity also has a strong dependence upon the ratio T_2/T_1 which results in the technique being most sensitive to those protons with considerable thermal motion, the mobile protons.

The time taken to produce these images ranged from 11 to 18 min. This should not be considered a fixed time. The time required depends upon the trade-off between image time and both noise and resolution. The data collection time increases as the square of the signal-to-noise ratio but falls rapidly with decreased resolution. The time required to obtain one line of the picture goes as the inverse fourth power of the resolvable transverse distance if the axial resolution, or slice thickness, and noise remain unchanged (Hinshaw, 1976). Thus reducing the array size from 128 to 100 would allow a 15 min. image to be obtained in about 4 min.

The equipment we used was designed to image one plane transverse to the axis of the sample chamber, but other arrangements are possible. Since the imaging is controlled electrically through field gradients and since no moving parts such as rotating gantries are required, enormous flexibility can be achieved. Sagittal planes are no more difficult to image than coronal planes. In fact the equipment could be designed to image any plane in any orientation. The thickness of the image plane is determined simply by the strength of the relevant gradient and thus the slice thickness can be increased, if necessary, to include the entire sample. It is possible to render the NMR spectrometer sensitive to only one small region of the sample. This would allow an image to be produced and then more detailed measurements, such as the measurement of relaxation times, to be performed at a chosen point in the image.

NMR relaxation times in biological tissue have received considerable attention in the literature (Knispel *et al.*, 1974; Hazlewood *et al.*, 1974; Hollis *et al.*, 1975). The differing relaxation times of tissue should aid in tissue identification, but the experimental overlap of data suggests that relaxation times alone are not enough. Further research is needed, however, particularly since past work has been done on excised tissue. Changes upon death and excision cannot be ruled out. There is also evidence that certain pathological conditions, such as oedema and ischemia, affect the tissue relaxation times. Fast growing tumours are reported to have relaxation times different from the host tissue.

The work reported here is based upon the resonance of protons, or hydrogen nuclei. The addition of water, for example, to an object while imaging mobile protons would be analoguous to the use of contrast media in X ray work. A second nucleus which gives a strong signal is the ^{19}F nucleus. Images based on the resonance of fluorine nuclei have recently been published (Holland *et al.*, 1977). Although fluorine exists in negligible quantities in most biological tissue, it can be introduced, for example, with fluorine-bearing drugs. It would then be possible to observe the physical distribution of the fluorine compounds without the interference of signals from naturally occurring material. Further applications are suggested by the recent research on animals using fluorocarbons as blood substitutes (Symposium on Artificial blood, 1975). Studying the distribution of fluorine with NMR would be analogous to observing the distribution of radioactive isotopes in body organs with a gamma camera.

There is no known hazard associated with NMR imaging. No ill effects have been observed on workers exposed for extended periods to static magnetic fields of up to 2 tesla (Barnothy, 1964, 1969). In the present system the average power density associated with the RF field during imaging is less than 2 mW/cm^3. If this system were modified to operate at 5 MHz and to accommodate a 30 cm diameter body, the expected average power density would be less than 0.7 mW/cm^3. This is to be compared with clinical diathermy which operates at exposures up to 600 mW/cm^2 and a recommended maximum long-term exposure of 10 mW/cm^2 (Johnson and Guy, 1972).

Image quality is very difficult to define. Even such apparently simple questions as the thickness of the slice become complex upon close examination. Studies made using simple phantoms made up of water, glass, and air are not very helpful and may even be misleading since real biological tissue contains a wide range of relaxation times. The entire question of objective image quality, including such problems as noise, geometric and intensity distortions, planar and axial resolution and artifacts, remains to be considered.

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Book reviews

Cross-sectional Anatomy: Computed Tomography and Ultrasound Correlation. By B. L. Carter, J. Morehead, S. M. Wolpert, S. B. Hammerschlag, H. J. Griffiths and P. C. Kahn, illus., 1977 (Appleton-Century-Crofts), £34·00.

Computerized Axial Tomography (An anatomic atlas of serial sections of the human body. Anatomy-Radiology-Scanner). sections of the human body. Anatomy-radiology-scanner). By J. Gambarelli, G. Guerinel, L. Chevrot and M. Mattei, pp. viii+286 illus., 1977 (Springer Verlag, Berlin), $105.60.

Computerized tomography has renewed interest in transverse cross-sectional anatomy of which there are several classical volumes. These two new books attempt to relate serial sections of frozen corpses to normal radiological appearances and are directed to the increasing numbers of radiologists who spend time endeavouring to interpret unfamiliar images produced by new technology.

Gambarelli and his colleagues have produced a book based on sections 1 cm apart. Typically the open book shows a colour photograph of the specimen on the left-hand page, with a diagram indicating the site of the slice. Opposite is a line drawing of the photograph with parts indicated by numbers, the key to which is on the lower left-hand page. Beneath the line drawing there is a smaller unlabelled radiograph of the specimen and a CT scan of a similar level with some numerical labelling.

The book by Carter and her colleagues is an elaboration of Eycleshymer and Schoemaker's classical "A Cross-Section Anatomy", with redrawn head-sections more closely related to the planes used in scanning. Typically an open page shows on the left leaf a body section of similar size to Gambarelli, as a line drawing both numbered and labelled. On the right-hand leaf are five small pictures, one is the body section viewed from below as seen conventionally in the scan. The others are CT images. These small images are unlabelled but there are explanatory legends. This is followed by a whole-page radiograph of a comparable body slice as conventionally viewed from the feet on the left-hand page with a group of small CT scans or ultrasound images on the opposite page.

Both books have small introductory sections on the principles of the technique and the Gambarelli book includes a section of mathematical theory which most radiologists would find difficult to understand.

The labelling of the larger images in the book by Carter is less easy to see but this is more than compensated by the labelled and reversed radiographs of similar sections. The CT scans are better labelled in Gambarelli but are fewer in number; the colour photographs of this work are superfluous in my opinion.

The inclusion of the supplementary radiographs of the sections orientated in the usual CT convention, a more comprehensive exposition of the limbs and vertebral column, the inclusion of some ultrasound images which are however very rudimentary and some sagittal sections make the book by Carter and her collaborators much the better buy. Both books, however, could well be improved by more adequately labelled scans.

D. G. SHAW

BJR Supplements

No.1	*Certain aspects of the action of radiation on living cells,* edited by F. G. Spear (1946)	£1·00
No.2	*Some applications of nuclear physics to medicine,* by W. V. Mayneord (1950)	£2·50 (Members £1·75)
No.4	*Cancer of the breast,* by D. W. Smiths, P. Rigby-Jones and D. A. G. Galton (1952)	£1·50 (Members £1·00)
No.9	*The spectra of X rays scattered in low atomic number materials,* by W. R. Bruce and H. E. Johns (1960)	£1·00 (Members 50p.)
No.11	*Central axis depth dose data for use in radiotherapy,* edited by M. Cohen, D. E. A. Jones and D. Greene (1972, 1st reprint 1974, 2nd reprint 1978)	£4·70 (Members £3·20) *
No.12	*Carcinogenesis and radiation risk: a biomathematical reconnaissance,* by W. V. Mayneord and R. H. Clarke (1975)	£6·50 (Members £4·75) †

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The British Journal of Radiology (1975) Supplement No.13

The Pathogenesis of Reflux Nephropathy

(Chronic atrophic pyelonephritis)

By Professor C. J. Hodson, F.R.C.P., F.R.C.R., T. M. J. Maling, M.B., B.Ch., M.C.R.A., F.R.C.R., P. J. McManamon, M.B., B.Ch., L.G.M.C., F.R.C.R. and M. G. Lewis, M.B., B.S., M.D., M.R.C.Path.

The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

These observations have been given a firm experimental basis by Professor Hodson and his associates. Their careful work on the growing pig has shown that the sites of intra-parenchymal or intra-renal reflux (I.R.R.) are the sites of subsequent scarring and atrophy. I.R.R. only occurs above a critical pressure level; reflux at lower-pressures produces no evident damage. Infection aggravates scarring but, in the presence of I.R.R., scarring can occur with sterile urine.

The work set out in this monograph has wide practical implications, and is of interest to paediatricians, nephrologists, urologists, radiologists and others concerned in the management of patients with urinary tract infection.

PRICE: £1·90 (Members of The British Institute of Radiology £1·75)

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1978, *British Journal of Radiology*, *51*, 281–285 APRIL 1978

Rectilinear bone scanning: differentiation between metastases and degenerative spinal disease

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(*Received April, 1977 and in revised form August, 1977*)

ABSTRACT

Criteria have been developed for radioisotope scanning of bone with an eight-colour-display rectilinear scanner, to differentiate metastases from degenerative spinal disease. If the area of increased uptake is two or more colours "hotter" than normal, this is probably due to metastases even if degenerative spinal disease coexists. The positivity of a scan due to degenerative spinal disease is a function of the degree of sclerosis adjacent to the intervertebral discs and apophyseal joints; it is not related to the degree of osteophyte formation.

The most frequent indication for bone scanning is the detection of metastases. It is a fact that both metastases and degenerative joint disease result in a positive scan (Merrick, 1975). It would be efficaciously and economically advantageous if these two common conditions could be differentiated on the basis of radionuclide uptake without recourse to radiology. In the appendicular skeleton the co-existence of these two pathologies is uncommon because metastases are relatively infrequent; when they do coexist, metastases rarely affect the epiphyses (Scott and Adams, 1975); Sutton and Grainger, 1975). However, in the spine where joints are superimposed upon vertebral bodies, can increased radionuclide uptake be ascribed as being due to metastases when there is coexistent joint disease?

The aims of this study are: firstly, to decide if metastases can be differentiated from degenerative spinal disease solely on the basis of radionuclide uptake, and secondly, in those cases in which the distinction cannot be made solely on the basis of radionuclide uptake, to decide if there are any useful differentiating radiological features.

MATERIALS AND METHODS

Methods of quantitation

The fundamental prerequisite for the objective interpretation of rectilinear scan images is a method of quantitation. Only when this exists can the criteria of normality and specific pathologies be developed.

The method of quantitation used in this study is predicated on the fact that the eight-colour scale of the scanner printout is linearly related to the intensity of the detected radiation. Thus, the colour print-out was represented by numbers (one to eight) and measurements were made at desired areas on the scan. The sensitivity was increased by interpolating half-scores: an area exhibiting an equal mixture of two colours scored the mean of the two colours. Normal scans were analysed as follows: the colour score of each vertebral body from D1 to the body of the sacrum was determined and the difference between the value of a vertebral body and the cranially adjacent vertebral body was calculated. This was repeated for each scan and a series of mean difference values between adjacent vertebrae, from the upper dorsal to the upper sacral spine, was obtained. Similar mean differences for symmetrical sites were calculated: humeral heads, sacral alae and femoral heads. In the abnormal scans, the magnitude of the difference between the pathological area and the adjacent normal area (or anatomically symmetrical site) was recorded.

Radiological scoring of the components of degenerative spinal disease.

In this study the term degenerative spinal disease (hereafter referred to as "O.A.") includes spondylosis of the intervertebral discs and osteoarthritis of the arthrodial joints. The components of O.A. which might reasonably contribute to the positivity of a scan were assumed to be osteophytic lipping, sclerosis in relation to the arthrodial joints and sclerosis adjacent to the disc spaces. The length of the osteophytes and the thickness of the zones of sclerosis were measured using a standard transparent centimetre ruler. In measuring the thickness of the zones of sclerosis the width of the arthrodial joints or the disc spaces were not included (Fig. 1).

Scanning technique

All scans were performed using ^{99}Tc^{m}-EHDP (Osteoscan, Proctor and Gamble Ltd.). The dose was 15 mCi and the interval between injection and

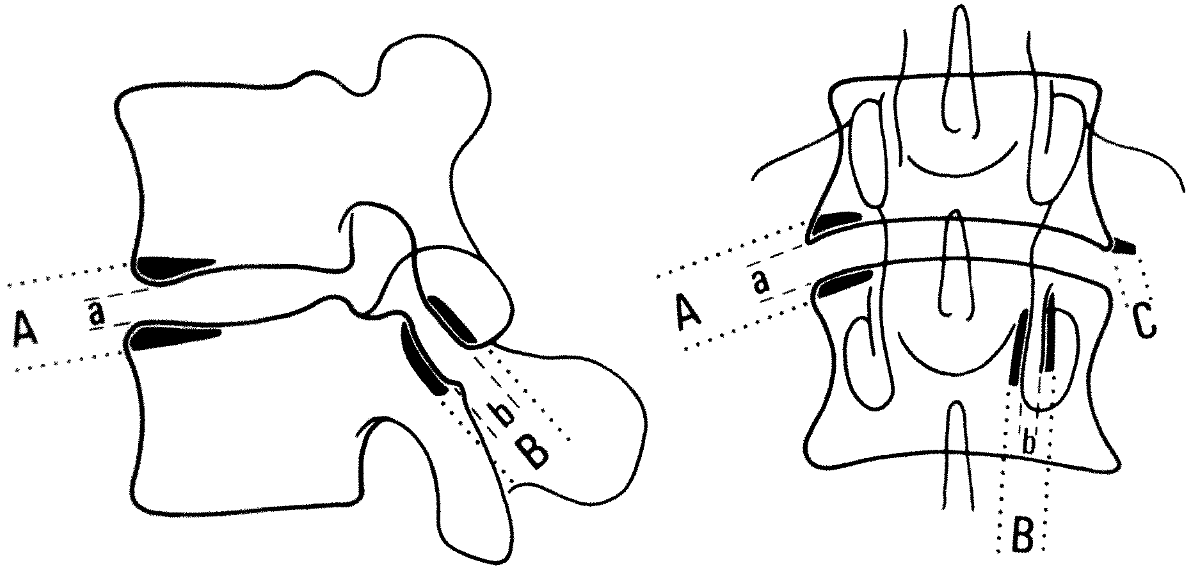

Fig. 1.

Measurements of O.A. The degree of sclerosis adjacent to the disc space or arthrodial joints in mm is given by (A–a) and (B–b) respectively. The width of the joint space is subtracted as it probably does not contribute to radionuclide uptake. The degree of osteophyte formation is given by C, the length of the osteophyte in mm. Measurements were made either on the A.P. or lateral film depending on which gave better demonstration of joint space.

scanning was three hours. The rectilinear scanner was a Selo DS4/4 (ICN Tracer-lab Ltd.). The scanner settings were calibrated such that the count rate from the hottest part of the spine (D2 to D6) was 60% of the operational range: green/yellow print-out. Other aspects of technique were standard (Merrick, 1975).

Selection of patients

Normal patients: All available normal bone scans and accompanying radiographs performed in 1973 and 1974 were reviewed. Further selection was based on the following criteria:

(a) normal bone scan report;
(b) accompanying radiographs showed no evidence of degenerative disease or other pathology;
(c) the patients had been followed-up for at least 18 months and remained free from malignant disease.

Thirty-seven patients satisfied these criteria and as a result of detailed study it was decided that to be considered abnormal the difference in uptake between adjacent vertebrae or symmetrical sites must be one or more colours (Fig. 2).

Patients with metastases and O.A.: A random selection was made of positive bone scan examinations performed in 1973 and 1974. Additionally, a random selection was made of patients with a normal scan and radiological evidence of O.A. Only those patients with available case sheets and corresponding radiographs were accepted for further study. Patients were deemed to suffer from metastatic bone disease if:

(a) there was unequivocal radiological evidence of metastases which corresponded to the area of increased uptake. Patients with positive bone scans who on follow-up for one year or more did not develop radiological evidence of malignancy corresponding to the increased uptake were excluded;
(b) There was unequivocal histological evidence of malignancy corresponding to the area of increased uptake. (Histology must have been obtained after the scan.)

Patients were deemed to suffer from O.A. if their radiographs showed the standard radiological signs, e.g. Sutton and Grainger (1975), and their subsequent clinical course and investigations failed to reveal any evidence of malignancy.

RESULTS

The distributions of intervertebral uptake differences for normals and patients with O.A. or metastases are shown in Fig. 2. Comparison of the normal patients and those with metastases shows that there is very little overlap. Only 7% of metastatic sites fall

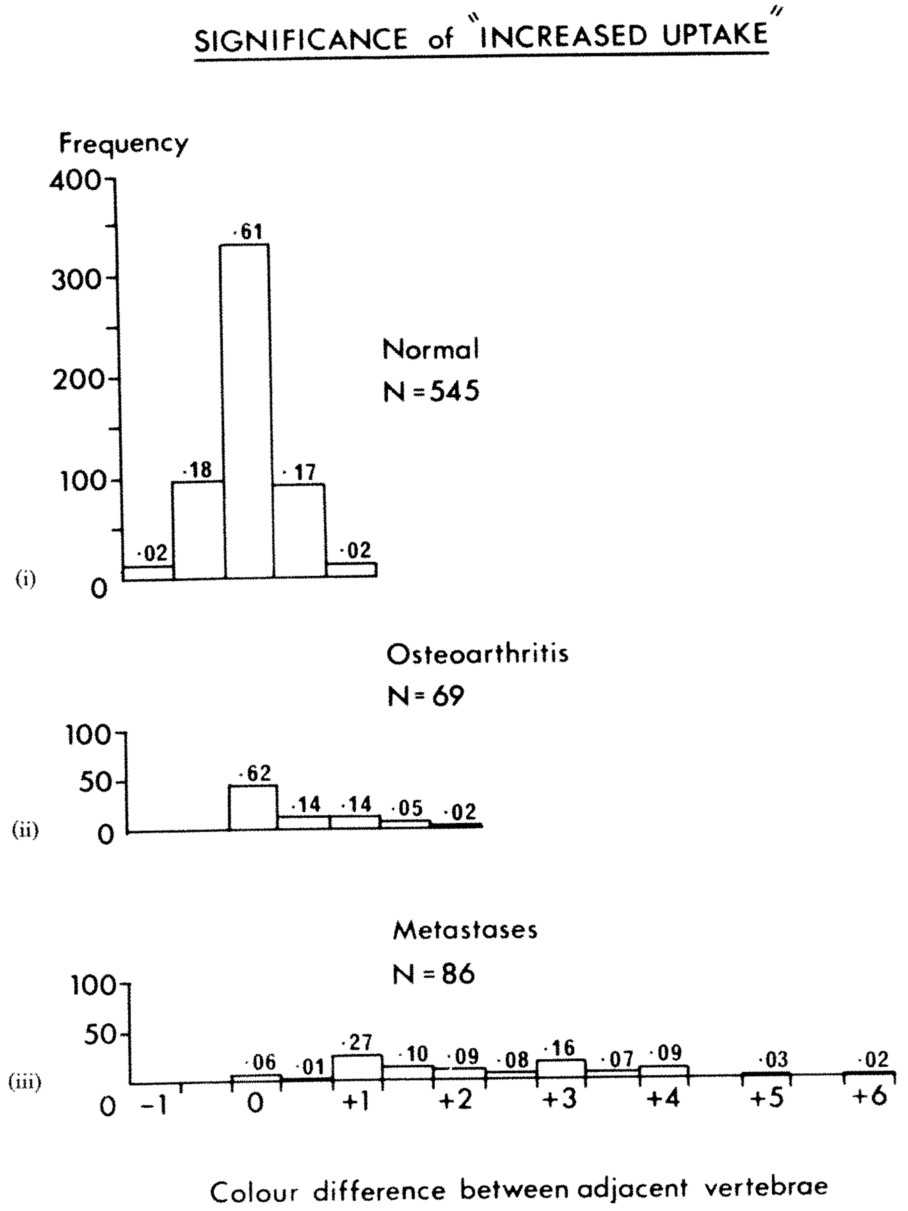

Fig. 2.

Intervetebral uptake differences. The colour scale at the bottom is common for all three histograms.

(i) Normal histogram. Sixty-one per cent of sites show no difference in uptake compared with adjacent area. A further 35% only vary within half a colour; this frequency is too great to be considered abnormal, therefore an area of interest has to be at least one colour hotter than the adjacent area to be considered abnormal.

(ii) Osteoarthritic histogram. Degenerative joint disease practically never causes an increase in uptake of two or more colours more than adjacent spine.

(iii) Metastases histogram. It should be noted that as the histograms have a common scale we can see that only 7% of metastases fall within the normal range.

within the normal range. The mean increase in uptake at sites with metastatic bone disease is about 2.5 colours more than the adjacent normal vertebrae.

In the O.A. group two important results emerge. First, the majority of patients have normal scans. Second, only 2% of patients with O.A. exhibit an increase in uptake greater than 1.5 colours. If we accept a 1.5 colour increase as a cut-off value, then

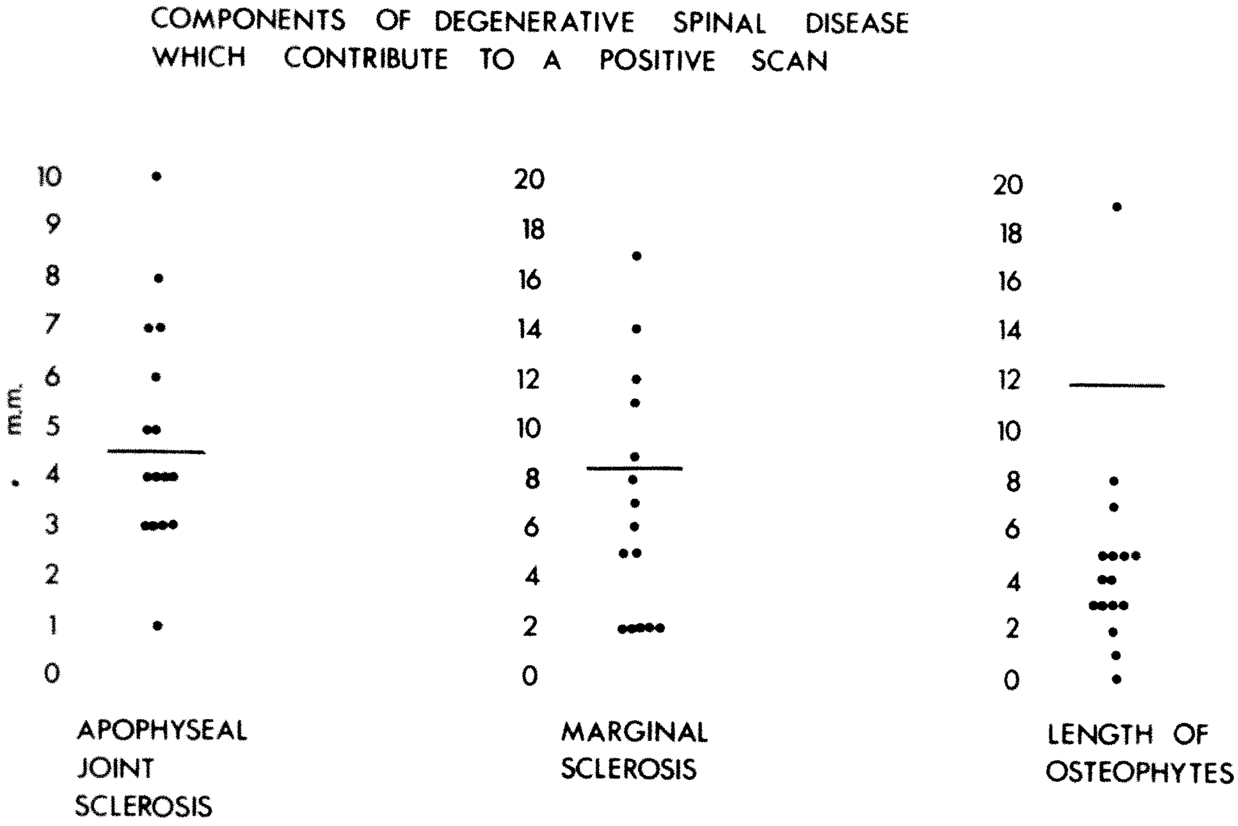

FIG. 3.

Components of degenerative spinal disease which contribute to a positive scan. The bars indicate the upper limits (+1·96 S.D.) not the means of values of those patients with negative scans and radiological evidence of O.A. In patients with positive scans due to O.A. the values for the degrees of sclerosis or osteophyte formation are indicated by the dots. Patients with positive scans have osteophytes of the same order of magnitude as those patients with negative scans. This suggests that osteophytes do not contribute to the positivity of a scan.

54% of metastases will exhibit uptakes which are too high to be due to O.A. Thus, an increase in uptake of two or more colours is not due to O.A.

The values for the length of the osteophytes and the thickness of the zones of sclerosis are given in Fig. 3. In the patients with normal scans and radiological evidence of O.A. the mean and + 1.96 standard deviation parameters were calculated. The + 1.96 limits are indicated by the bars. In patients with positive scans and radiological evidence of O.A., the individual measurements are illustrated as dots. As patients with positive scans have osteophytes of the same order of magnitude as those with negative scans it is unlikely that osteophyte formation significantly contributes to the positivity of a scan. It should also be remembered that the bars indicate the upper limit of O.A. not accompanied by a positive scan. Thus, the position of the dots relative to the bars suggests that it is only a moderately severe or marked degrees of sclerosis which will be accompanied by a positive scan. The cut-off values for the degree of sclerosis in relation to the arthrodial joints or disc margins above which a scan will be positive are 4.5 mm and 8.5 mm respectively.

DISCUSSION

The differentiation between malignancy and O.A. is a fundamental problem in rectilinear scan interpretation. Elegant studies quantitating uptake in arthritis by Bauer and Smith (1969) and DeFiore *et al.* (1970) unfortunately suffer from the following disadvantages. First, the techniques used have been rendered obsolete by recent advances in radiopharmaceuticals and instrumentation. Second, parameters and techniques of measurement, although perfectly valid, were too complicated for use in the interpretation of routine scans.

TABLE I

Number of Lesions	The probability of one or more lesions exhibiting an increase in uptake of two or more colours.
1	0·5
2	0·75
3	0·88
4	0·94
5	0·97

The present study, predicated on a simple method of quantitation, enables a confident discrimination to be made between metastases and O.A. in just over 50% of metastases. It is emphasised that this discrimination is based solely on the magnitude of uptake at a single site. However, it has been shown that 86% of patients with bone metastases have multiple lesions (Shirazi *et al.*, 1974). Therefore, as we only need to diagnose one lesion as malignant to confirm bone metastases, the probability of multiple lesions being due to malignancy can be calculated by the binomial distribution (Table I).

It is further emphasised that the site of the increased uptake influences the probability of malignant bone disease. If any of the lesions are related to the metaphysis or diaphysis of adjacent long bones then the problem of differentiation from O.A. does not occur. Although the differential diagnosis extends beyond O.A. and metastases, the pattern of scan abnormalities and the clinical history will indicate when the less probable alternatives should be considered.

The 7% false negative rate accords with the results of others (Ell *et al.*, 1976). It is felt that this is probably due to some patients being on hormonal- or chemo-therapy at the time of scanning.

It is in the remaining 39% (100%−54%−7%) of metastatic sites in which the radionuclide uptake is not sufficiently great to permit a confident diagnosis of metastases that false-positive results occur. The incidence of false-positive studies can only be minimized if there is careful correlation between the scan and the radiological findings.

Radiologists generally equate osteophytic lipping with osteo-arthritis or spondylosis. However, the present results suggest that when the radiologist is evaluating the cause of a positive bone scan he should ignore osteophytes and concentrate on sclerosis adjacent to the intervertebral discs or apophyseal joints. These findings support the work of Bauer and Smith (1969). It is also suggested that only moderate or advanced degrees of O.A. give rise to a positive scan. Thus, although no firm probabilities are offered, the more normal the radiological appearances the less the probability of a false-positive diagnosis of metastatic bone disease. It is not possible to estimate the proportion of patients with O.A. exhibiting a positive scan because it would vary widely according to the defining criteria for O.A.

Ideally there should be interdisciplinary discussion at all stages of patient management. It is emphasised that imperfect communication can lead to false-positive scan diagnosis in two particular situations. First, if O.A. changes are present and not reported then the clinician will justifiably assume that the positive scan is due to malignancy. Second, if osteophytic lipping or other radiological signs are over emphasised then the clinician may falsely assume that the positive scan is due to O.A.

The following aspects of our normal criterion require amplification. The sex and age distributions of the normal, O.A. and metastases group were similar. Our normal criterion was validated by observing a further three normal samples: each sample consisted of 100 randomly chosen sites. The dominant influence on an abnormal scan must be the underlying pathology. Other factors such as the physical conditions of the examination are merely relevant. Our criterion of normality is probably applicable to other departments with similar, rather than identical, scanning techniques.

The conclusions of this study are not applicable to gamma-camera examinations. This is because the physical conditions of the two techniques are completely different. Further work is in progress trying to establish similar criteria for gamma-camera examinations.

ACKNOWLEDGMENTS

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Central airways obstruction in carcinoma of the bronchus treated by radiotherapy: a study of pulmonary function

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Abstract

A battery of lung function tests was performed on 28 patients with carcinoma of the bronchus, before radiotherapy, six weeks later, and at three months.

Twenty-five had evidence of airways obstruction, though only five had a forced expiratory ratio of less than 50%. Nine were shown to have obstruction to a main or lobar bronchus, while 11 definitely did not, but the only significant difference in lung function between groups was in the residual volume calculated from single breath helium dilution. Eight of ten cases of squamous cell carcinoma were central, and seven of these obstructive. Of seven cases with undifferentiated cells only two were central ($p < 0.05$) and one obstructive. Breathlessness on presentation was significantly more common in patients with central tumours (6/12) than those with peripheral lesions (1/8), and all six breathless patients with central tumours claimed that this symptom improved after radiotherapy.

Radiotherapy may have a palliative effect for breathlessness in patients with central airways obstruction due to tumour.

In 1975 Caplin and Festenstein reported a low incidence of severe airways obstruction in a group of patients with carcinoma of the bronchus. Suspecting that this finding was due to bias in selection, we repeated the study in an overtly selected group where incidence of airways obstruction might be expected to be higher, namely patients with bronchial carcinoma referred for radiotherapy.

A second purpose of this study was to see if by using a wide selection of techniques of measuring lung function we might find criteria for detecting obstruction in central airways (trachea and major bronchi), and to see how the measurements changed after radiotherapy, although we recognized that it would have complicated effects on lung function apart from the possible amelioration of a localized obstruction (Deeley, 1960; Emirgil and Heinemann, 1961; Axford *et al.*, 1977).

During the study we noticed a difference in the incidence of breathlessness in groups of patients with and without central obstruction and that the dyspnoea of patients with central obstruction was apparently relieved by radiotherapy.

Patients

Fourty-four patients with carcinoma of the bronchus were referred to the Department of Radiotherapy, Middlesex Hospital (Dr. Margaret Spittle) and received a split course of radiation, 3000 rad in ten treatments over 12 days on a radioactive cobalt machine, followed by a break of four weeks and then a further 3000 rad in ten treatments over 14 days on the 8 MeV linear accelerator, the treatment field being arranged to avoid the spinal cord. In addition they took part in a trial of a cytotoxic drug ICRF 159 (Razoxone) 125 mg b.d., being randomly assigned to control or drug-treatment groups. Subsequent analysis showed no effect on survival rate from cytotoxic therapy (Spittle, in preparation), and the results have been pooled for the lung function analysis.

While all patients had some simple lung function tests as part of the assessment of cytotoxic therapy, they were excluded from the full series of tests:

(1) if they were too sick, frail, or elderly to complete all the tests without distress;
(2) if they were unable to cooperate in the necessary respiratory manoeuvres;
(3) if these manoeuvres caused or exacerbated chest pain;
(4) if a lobar or main bronchus was completely blocked (as opposed to narrowed).

Of the 44 patients considered, 16 were excluded on these grounds and the remaining 28 were classified in three groups:

Group 1 "Central obstructive" (nine patients)

These subjects had narrowing of a main or lobar bronchus seen at bronchoscopy in eight cases and by tomography in one.

Group 2 (A) "Central non-obstructive" (three patients)

(B) "Peripheral" (eight patients)

They had bronchoscopies which were normal or showed changes at the segmental level, with a central mass on the chest film in Group 2(A), and a peripheral mass in Group 2(B).

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Group 3 "Unclassified" (eight patients)

The remaining patients could not be assigned with certainty to either of the first two groups, and results obtained from them are used only in considering the incidence of airways obstruction in the whole series of 28 patients.

METHODS

The patients attended the lung function laboratory first before radiotherapy; second, six weeks later, before the second part of the split course; and finally at three months, one month after completion of the course. Three patients attended only for the first two appointments, and two for the first and third only, being too ill to come on the other occasion.

The following measurements were obtained in the same order at each attendance:

(1) Transfer factor for carbon monoxide ($T_{L_{co}}$) by the single-breath technique (Cotes, 1975a). This method incorporates the calculation of residual volume from the distribution of the tracer gas helium in the inspirate (RV_{He}).

(2) Peak expiratory flow rate (PEF) and peak inspiratory flow rate (PIF) with a Wright peak flow meter adapted according to Nairn and McNeill (1963).

(3) Vital capacity (VC), forced expiratory volume in one second (FEV_1) and the forced expiratory ratio (FEV_1/VC) with a dry spirometer.

(4) Residual volume (RV), total lung capacity (TLC), and the ratio RV/TLC by body plethysmography (Dubois *et al.*, 1956a).

(5) Airways resistance (R_{AW}) and specific conductance (SG_{AW}) by body plethysmography (Dubois *et al.*, 1956b).

(6) The maximum expiratory flow volume (MEFV) loop (Pride, 1971). We took the peak flow from the loop and the maximum expiratory flow at 50% VC and calculated the ratio MEF_{50}/PEF.

(7) In patients with abnormal airways resistance, PEF and FEV_1 were measured again after the patient had inhaled a bronchodilator drug.

Symptoms recorded in Table I were recorded systematically before, during and after treatment, but a standard questionnaire was not used to determine the degree of breathlessness. Improvement in breathlessness was recorded if the patient noted less dyspnoea on effort or at rest.

TABLE I

CLINICAL DETAILS

							Presenting features					
	No.	Age	Sex	Cell type	Chronic bronchitis	Smoker or ex-smoker	Breathless	Pain	Haemoptysis	Cough	Weight loss	CXR only
Group 1 Central obstruction	1.	71	M	SQ	+	+	+	—	—	—	—	—
	2.	61	M	U(S)	—	+	+	+	+	+	—	—
	3.	50	M	SQ	—	+	—	—	+	—	—	—
	4.	54	M	SQ	+	+	—	—	—	+	—	—
	5.	61	M	AD	+	+	—	—	—	—	—	+
	6.	77	M	SQ	+	+	+	—	+	+	—	—
	7.	69	M	SQ	+	+	+	—	—	—	—	—
	8.	70	M	SQ	+	+	+	—	—	—	+	—
	9.	60	M	SQ	+	+	—	—	+	—	—	—
Group 2A Central, no obstruction	10.	67	M	SQ	—	+	—	—	—	—	—	+
	11.	55	M	NK	?	+	+	—	—	+	—	—
	12.	55	F	U(L)	+	+	—	—	+	—	—	—
Group 2B Peripheral, no obstruction	13.	68	M	SQ	+	+	—	—	—	—	—	+
	14.	68	M	NK	+	+	—	+	—	—	+	—
	15.	73	M	U(S)	+	+	—	—	—	+	+	—
	16.	55	M	U	—	+	—	—	—	—	—	+
	17.	62	M	U	—	+	+	—	—	—	+	—
	18.	55	M	U(S)	—	+	—	+	—	—	—	—
	19.	56	M	U(S)	+	+	—	—	—	+	—	—
	20.	52	F	SQ	—	+	—	—	+	+	—	—

Cell type: SQ = squamous cell carcinoma; AD = adenocarcinoma; U = Undifferentiated, with (S) signifying small cell type and (L) large cell; NK = not known.
Presenting features: "CXR" = tumour detected on chest film in a symptomless patient.

TABLE II

Initial lung function

	No.	PEF l/min	PIF l/min	FEV_1 l	VC l	FEV_1/VC %	R_{AW} kPa l^{-1} sec	SG_{AW} kPa^{-1} sec^{-1}
Whole series	28	335 (96)	303 (95)	2.20 (0.69)	3.48 (0.56)	63 (14)	0.2 (0.09)	0.81 (1.27)
%predicted normal		58	—	77	89	90	—	—
Group 1	9	337 (95)	309 (103)	2.06 (0.46)	3.37 (0.26)	62 (11)	0.19 (0.1)	1.3 (0.8)
Group 2	11	338 (114)	299 (76)	2.29 (0.93)	3.65 (0.6)	61 (18)	0.21 (0.8)	1.1 (0.6)
		T_{Lco} mmol $min^{-1}kPa^{-1}$	RV_{He} l	RV l	TLC l	RV/TLC %	MEF_{50} l/sec	MEF_{50}/PEF %
Whole series	28	6.1 (1.7)	1.65 (0.74)	2.95 (0.129)	6.48 (1.26)	45 (11)	1.82 (1.35)	0.318 (0.124)
% predicted normal		71	—	131	104	117	33	—
Group 1	9	5.3 (1.4)	*1.22 (0.27)	2.86 (0.69)	6.37 (0.69)	45 (7)	1.78 (1.28)	0.312 (0.141)
Group 2	11	6.6 (1.8)	2.14(0.79)	3.18 (1.23)	6.83 (1.17)	45 (11)	1.90 (1.65)	0.321 (0.226)

Lung function results: mean values with one standard deviation in brackets. Normal values are taken from Cotes (1975b) except for MEF_{50} (Bass, 1973). Normal range for R_{AW} is 0.05 to 0.2, for SG_{AW} 1.3 to 3.5.
*Difference between means significant at 5% level by paired t-test.

The clinical details of the patients were not known to the persons performing the lung function tests.

Results

Some clinical details of patients in Groups 1 and 2 are given in Table I. Eight out of ten cases of squamous cell carcinoma had central tumours and of these seven were obstructive; whereas of seven cases with undifferentiated cells, only two were central and one obstructive. This difference in central *v.* peripheral distribution of the two tumour types is significant at the 5% level (χ^2 test, one degree of freedom).

Twelve patients had productive cough on most days for at least three months of the year for at least two years, and were designated as having chronic bronchitis. All patients were or had been smokers.

Breathlessness on presentation was notably more common in patients with central tumours (6/12) than in those with peripheral lesions (1/8, $P < 0.05$ by χ^2 test). All six patients with central tumours said their breathlessness was improved after radiotherapy, whereas the single breathless patient with a peripheral carcinoma did not.

Initial lung function (Table II)

Most of the patients had obvious airways obstruction, and mean results for the group as a whole show the characteristic low PEF, FEV_1 and FEV_1/VC, with raised RV and RV/TLC signifying hyperinflation. Fifteen of the 28 patients had a forced expiratory ratio of less than 65%. Of the remaining 13, ten had either a ratio for RV/TLC of more than 120% predicted normal; or R_{AW} greater than 0.2 kPa l^{-1} sec; or SG_{AW} less than 1.3 kPa^{-1} sec^{-1}; or MEF_{50} less than 60% predicted normal; or some combination of these abnormalities. Thus, only three of the 28 subjects had no evidence of airways obstruction.

There was no significant difference between means in Groups 1 and 2 for any measurement except RV_{He}, where the patients with central obstruction had a lower mean value (1.22 l) than those without (2.14 l).

Lung function at three weeks and six months

Mean results for the first (pre-treatment) attendance were compared with those at six weeks and three months by paired *t*-test. There were no significant changes in any measurement (including RV_{He}) for the entire series of 28 patients or for Groups 1 and 2 taken separately. The only trend approaching significance was in T_{LCO}, which decreased by 1.1 mmol min^{-1} kPa^{-1} at three months in the whole series, and by 1.5 mmol min^{-1} kPa^{-1} in Group 2.

Bronchodilator effect

No patient had a history suggestive of asthma. Five patients had an increase of PEF and FEV_1 of more than 10% on one occasion, two showed such increases twice, and one on three occasions.

Discussion

Fifteen of our 28 patients had a low forced expiratory ratio (FEV_1/FVC) and ten had definite but more subtle evidence of airways obstruction, particularly marked in the maximum expiratory flow at 50% VC. Only three had normal airway function.

The mean forced expiratory ratio for our patients was 63%, similar to the figure of 61% obtained by Caplin and Festenstein (1975) and to the 65% found by Legge and Palmer (1973). FEV_1/FVC was less than 50% in five (18%) of our patients, and in 16% of those studied by Caplin and Festenstein (1975). These workers felt that the prevalence of severe airways obstruction ($FEV_1/FVC < 50\%$) in patients with carcinoma was low, when they were compared with chronic bronchitis subjects of similar age with comparable duration of productive cough. Their series refers to patients considered for surgery where patients with severe respiratory disability may have missed selection, whereas ours were referred specifically for radiotherapy, and presumably younger and fitter patients with operable tumours were excluded. We were surprised to find that our results for forced expiratory ratio, which was their only measurement, are similar to theirs.

We would prefer to stress the commonness in patients with bronchial carcinoma of mild or moderate airways obstruction, the incidence of which effectively impeded the search for lung function criteria of central airway narrowing in our patients. Caplin and Festenstein do not refer to this aspect, while Legge and Palmer (1973) surprisingly state that airways obstruction due to large centrally placed tumours was not seen in their series of 330 patients with bronchial carcinoma.

A fixed expiratory obstruction in central airways may decrease PEF without altering maximum flow in the later part of forced expiration (Harrison, 1976); we examined MEF_{50}/PEF believing that the ratio might be higher in the group with central obstruction, but there was wide inter-subject variation and no significant difference. A more recently developed technique which tests the effect of breathing a helium-oxygen mixture on maximum expiratory flows might well have helped to distinguish localized narrowing in central airways from diffuse peripheral obstruction (Despas *et al.*, 1972) but it was not available at the time of the study.

When measuring transfer factor (diffusing capacity) for carbon monoxide by the single breath technique, a helium tracer is included in the inspirate; from the inspired concentration of helium and the concentration on the alveolar plateau recorded during expiration the "effective" volume in which the carbon monoxide is diluted can be calculated. RV_{He} is derived from this volume and was significantly lower in patients with central obstruction. The difference between RV_{He} and true RV by plethysmography represents a poorly ventilated lung volume (1.6 l in Group 1 and 1.0 l in Group 2, Table II). Our findings could be explained if we assume the presence of a large poorly ventilated volume of lung behind the central constriction which would receive very little helium during a single breath but which would be accurately measured by plethysmography. On the other hand Simonsson and Malmberg (1964) found no alteration of the single breath nitrogen washout plateau in patients with central obstructive tumours.

We could find no significant changes in mean lung function measurements (including RV_{He} and the difference between RV and RV_{He}) over the three month period of observation. Deeley (1960) showed radiological evidence of lung shrinkage in patients with carcinoma of the bronchus two months after a course of 4500 rad, with small increases in VC and maximum breathing capacity. It is not clear how many of his subjects had chronic peripheral airways obstruction. Emirgil and Heinemann (1961) found in their patients after radiotherapy early and progressive reduction of RV and TLC with normal RV/TLC ratio, and a fall in T_{LCO} at 60 to 160 days which was sometimes transient. Eleven of their 15 patients were treated for mammary carcinoma and had presumably normal lungs, when the effect of radiation alone could be more precisely studied.

We were surprised by the correlation between central obstruction and breathlessness as a presenting symptom, and all patients with this combination claimed that their breathing was improved after treatment. Breathlessness is not normally regarded as a symptom which can be improved by radiotherapy and we can only speculate about mechanisms by which it may be relieved. In general any increased respiratory load, either resistive (airways obstruction) or elastic (pulmonary fibrosis or infiltration) may cause dyspnoea. Certainly we would not expect radiotherapy to improve breathlessness due to the latter cause, but it is conceivable that relief of a central airways block might do so—yet there was no uniform evidence that airways resistance (or RV_{He}) was improved by radiotherapy.

Whatever the mechanism, we conclude that radiotherapy may have a palliative effect on breathlessness in patients without widespread tumour infiltration but with central obstruction to large airways.

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We are most grateful to Dr. Margaret Spittle for permitting us to study her patients, and for criticizing the manuscript.

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Book review

Current concepts in radiology. Vol. 3. Edited by E. James Potchen, pp. xvi+453, 487 illus., 1977 (C. V. Mosby Co., Saint Louis; Distributed in U.K. by Henry Kimpton), £32·10.

This is a collection of 17 pieces by 35 authors, ranging very widely from chapter one "Information systems in departmental operations" to chapter 17 "Evaluation of diagnostic screening tests: a case study in hypertension". The subjects include computed tomography (four chapters), detection of breast cancer and of thrombus, radionuclide imaging of bone, myocardium and liver. There are 3 chapters on pulmonary topics: pleural effusions, linear shadows on chest X rays, and electrocoagulation of small lung tumours.

The editor hopes that "the essays provide a somewhat balanced appreciation of the excitement engendered by re-evaluation of past experiences in an amalgamation of the newer technologies". This is therefore by design a very mixed bag. Some pieces are luxury items that would not readily be chosen by workaday radiologists, for instance a chapter on "Comparative radiology: dysplasias of the canine forelimb". One chapter on departmental organization is a theoretical catalogue of "Problem identification and solution", with sentences like "The parameters of the reference data available for input are contained in a synoptic lexicon of anatomic, pathologic, support, and related functional terms".

It does not make me a chauvinist reviewer, I think, if the one radiologist contributor from this country stands out like a jewel: David Trapnell on "Linear shadows in chest radiographs". This is a splendid chapter, informative and stylish, with more science in its author's little finger than in the leaden heads of some other contributors.

There are two big chapters reviewing their authors' long clinical and experimental preoccupations. Both have "some" in their titles—can I found a club for people who forswear this feeble, meaningless adjective in medicine? I very much enjoyed Joseph Whalen and his colleagues from Cornell University on "Some metabolic considerations in bone disease". They grasp the opportunity offered by this sort of volume: of carefully simplifying and summing up the work and thought of several years. They have written a good current guide to metabolic bone disease, stimulating and nicely controversial (*e.g.* on osteoporosis). Everette James and Hugh Davson on "Some basic considerations of cerebrospinal fluid physiology as reflected by CSF imaging" also deal with several years' work, mainly on communicating hydrocephalus. Though their studies are interesting, they are less successful in guiding the reader through the maze. Their last section "CSF drainage and absorption", for instance, is 20 pages of continuous text and illustrations without a single subheading.

The last chapter on the care and cost of investigating patients with hypertension is a delightful summary of Barbara McNeil's and James Adelstein's remarkable 1975 work from Harvard.

A handful of chapters in this volume strike me as excellent. These are probably just enough to make larger libraries consider the book, but it costs £32·10.

THOMAS SHERWOOD.

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Response of selected tumour cell populations separated from a fibrosarcoma following irradiation *in situ* with fast neutrons*

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ABSTRACT

We have characterized selected populations of fibrosarcoma cells separated on density gradients of Renografin with respect to distribution in the cell cycle, clonogenic ability, and response to radiation. The latter two parameters have been observed to be related to the density of the cells, the denser populations being less clonogenic but more resistant to both low and high LET radiation. We have determined that these cells effectively repair potentially lethal damage if allowed to remain *in situ* following exposure to low LET radiation. This repair ability is not observed, however, following neutron irradiation. In addition, cells left *in situ* are relatively more sensitive to low doses of either low or high LET radiation. This difference in response is believed to be due to differences in the expression of damage by cells left *in situ* as compared to those assayed immediately. These data reflect the usefulness of cell separation methods in the study of solid tumour systems. Specifically, these methods reduce the heterogeneity found in the solid tumour by allowing for the isolation of subpopulations which then can be studied either individually or in relation to the entire tumour.

The response of selected tumour cell populations separated from a murine fibrosarcoma (FSa) and irradiated *in situ* with cyclotron-generated neutrons is described in this communication. The eradication or control of solid tumours growing in either human or animal hosts by radiation therapy is the result of the successful destruction or sterilization of all of the clonogenic cells present. While the primary tumour mass can be considered as a single entity, it is actually a complex and heterogenous cell system composed of neoplastic cells existing under a variety of physiological conditions. These include, in part, proliferating tumour cells amply supplied with the essential nutritional requirements for growth, non-proliferating or G_0 tumour cells which under the proper conditions might be recruited to re-enter a proliferative phase, and tumour cells which are about to lyse or die. Coupled with the above conditions are differences in the oxygen tension to which the various classes of cells are exposed. And, finally, variations in pH and differences with respect to cell-to-cell contact also exist and can affect the radiation response of cells within the environment of the tumour. All of these factors can have an effect on the radiocurability of the tumour.

With the advent of cell separation techniques, selected cell populations can be separated from complex cell systems such as solid tumours and studied individually. These separation procedures, developed to exploit certain physical differences which exist between morphologically similar cells, are based on the premise that variations in physical parameters such as density, size, and shape may also be indicative of functional differences. Enriched populations of clonogenic tumour cells have been successfully separated from disaggregated solid tumours by means of density (Pertoft, 1970) and velocity (Pretlow and Boone, 1970) gradient centrifugation. We have previously described in detail a procedure for the separation of at least five populations of cells, each differing in clonogenic ability, from a murine fibrosarcoma, by equilibrium density centrifugation using Renografin as the separation medium (Grdina *et al.*, 1975). Two of these populations, as well as the unseparated tumour population, were further characterized with respect to their response to ionizing radiation (Grdina *et al.*, 1976). These two populations designated band 2, $\bar{\rho}=1.08$ g/cm^3, and band 4, $\bar{\rho}=1.14$ g/cm^3, were separated after exposure of the FSa tumour *in situ* to ^{137}Cs γ radiation, and each differed in its response to irradiation. The band 2 population had a relatively large fraction of sensitive cells and a more resistant component, presumably hypoxic, whose response was apparent at doses greater than 1000 rad. Under conditions of acute hypoxia, however, all of the cells in this population became significantly more radioresistant. In contrast, the band 4 population consisted of relatively radioresistant cells which, even under conditions of acute hypoxia, exhibited no

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Animals utilized in this study were maintained in facilities approved by the American Association for Accreditation of Laboratory Animal Care, and in accordance with current United States Department of Agriculture and Department of Health, Education, and Welfare, National Institutes of Health regulations and standards.

change in radiation sensitivity. We have now characterized the response of these populations to irradiation *in situ* with fast neutrons generated at the Texas A&M University variable energy cyclotron (TAMVEC).

Implanted tumours were irradiated with fast neutrons or ^{137}Cs γ rays. After irradiation the tumours were excised and tumour cells were made into single-cell suspensions for assay of reproductive integrity. Recovery from potentially lethal damage was studied by excising the tumours immediately or six hours after irradiation. Survival was tested by lung-colony assay in mice which had received whole-body irradiation plus syngeneic bone-marrow cells. Aliquots of the tumour-cell suspensions were separated on density-gradients into two groups (band 2 and band 4) before assay by the lung-colony technique. Other aliquots were assayed by flow microfluorometry in order to determine the age distribution of irradiated cells.

MATERIALS AND METHODS

Mice and Tumours

Female C$_3$Hf/Bu mice from our specific pathogen-free breeding colony were eight to ten weeks old at the beginning of each experiment. Animals were kept five or six to a cage and maintained on a sterilized pellet diet and sterile water.

Fourth-generation isotransplants of a methylcholanthrene-induced fibrosarcoma were stored in a liquid nitrogen refrigerator, and experiments were restricted to tumours of the fifth generation. Tumour cells were implanted subcutaneously (sc) into each of the hindlegs of the test animals. All experiments were performed using tumours 12–14 mm in diameter.

Irradiation

Mice to be used in a lung colony assay were whole-body irradiated (WBI) with 1000 rad of γ rays from a single ^{137}Cs source, at a dose rate of 295 rad/min., one day prior to inoculation of tumour cells. This was done to increase the efficiency of the lung colony assay (Grdina *et al.*, 1975). Each WBI mouse was injected intravenously (iv) with 5×10^6 syngeneic bone marrow cells two hours after irradiation.

Neutron irradiations were performed at Texas A&M University using the variable energy 88 inch cyclotron (TAMVEC) following procedures described elsewhere (Withers *et al.*, 1974a). Briefly, neutrons having a mean energy of 22 MeV were produced by bombarding a beryllium target with a beam of 50 MeV deuterons [$E_d = 50$ MeV (Be)]. The energy designation to be used in this report refers to the energy of the incident deutrons. The dose in rads ($n+\gamma$) was computed using the Bragg-Gray relationship following methods described elsewhere (Almond *et al.*, 1973). The gamma contribution to the total dose was about 5% (Almond *et al.*, 1973). The doses expressed are the total neutron+γ-ray doses, and the dose rate was 90 rad/min. Exposures were monitored by two back to back sealed transmission chambers connected to integrators and placed in the neutron beam (Withers *et al.*, 1974b).

Tumour-bearing mice used in these experiments with neutrons were positioned individually in eight Lucite chambers within a 15 cm diameter circle on the front face of a 40 cm cubical Lucite tank containing tissue-equivalent liquid (Frigerio *et al.*, 1972). The distance from the target to surface of the Lucite (Perspex) mouse holder was 140 cm.

The γ-ray irradiations of tumour-bearing mice were performed at M.D. Anderson Hospital and Tumor Institute using a dual-source ^{137}Cs unit (AECL) (Hranitzky *et al.*, 1973). The dose rate was about 1060 rad/min as determined by lithium fluoride thermoluminescent dosimetry. All animals were irradiated in air without anaesthesia.

Bone marrow and tumour cell suspension

Donor C$_3$Hf/bu mice were sacrificed and bone marrow from their tibias and femurs was removed by forcing medium 199 (Difco Laboratories, Inc., Detroit, Michigan) through a 26-gauge needle into the marrow cavity. About 5×10^6 viable nucleated bone marrow cells were then injected into the lateral tail vein of each WBI mouse.

After exposure to selected doses of radiation, four to six tumours in each group were made into single cell suspensions following a method described in detail elsewhere (Grdina *et al.*, 1976). In brief, selected non-necrotic tumour tissue was finely minced and subjected to digestion for 20 min at room temperature with trypsin made up to 0.025% in Solution A (8.0 g NaCl, 0.4 g KCl, 1.0 g glucose, and 0.35 g NaHCO$_3$ in one litre of water). DNase (Deoxyribonuclease 1, crude beef pancreas; Sigma Chemical Company, St. Louis, Mo.) was also added to a final concentration of 0.1 mg/ml. After 15 min of stirring, the undigested tissue was allowed to settle to the bottom of the beaker, and the upper two-thirds of the suspension was removed and mixed with an equal volume of medium 199 supplemented with 5% heat-inactivated fetal calf serum. The suspension was passed through a stainless steel mesh (80 wires/cm) and then centrifuged twice at 225 g for five minutes. The supernatant was discarded and the cell pellet was resuspended in medium 199 with 5% serum.

All cell counts were performed using a haemaocytometer, and those cells which appeared morphologically normal under phase contrast microscopy were counted as viable. Throughout the range of radiation doses used, the cells counted as viable in the resulting suspension were routinely found to be greater than 95%, and the yield of cells was about 10^8 per g of excised tumour tissue.

Gradients

Tumour cells were separated on sterile preformed density gradients of Renografin-60 (methyl-glucamine N, N'-diacetyl-3, 5-diamino 2, 4, 6-tri-iodobenzoate, E. R. Squibb and Sons, New York, N.Y.) following a procedure described in detail elsewhere (Grdina *et al.*, 1975). Because of the lack of the necessary facilities available to us at the Texas A&M cyclotron installation, all cell separations had to be performed at M.D. Anderson Hospital and Tumor Institute. This necessitated a delay of four to six hours from the time of neutron irradiation of the tumour-bearing mice to the time at which they were sacrificed. Experiments involving unseparated tumour cell suspensions were performed both at Texas A & M and at M.D. Anderson.

Between 5×10^7 and 8×10^7 viable cells were separated in 34 ml gradients of 10 to 35% Renografin diluted with Ringer's solution, USP (Baxter Laboratories, Division of Travenol Laboratories, Inc., Morton Grove, III.). Gradients were centrifuged for 30 min in SW27 tubes at 10000 RPM (about 13000 g) at 4°C in a Beckman model L5-50 preparative ultracentrifuge. The selected cell populations, bands 2 and 4, were removed by introducing

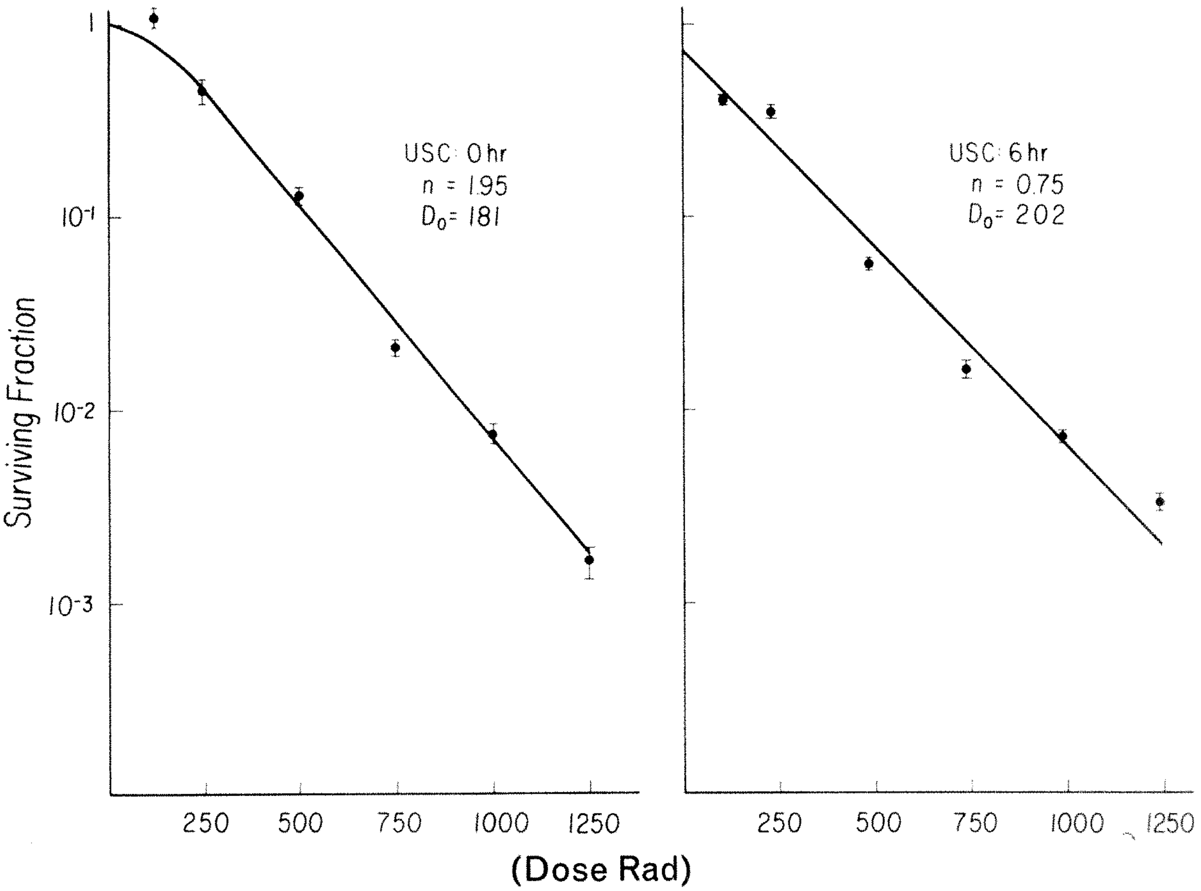

FIG. 1.

Survival curves for unseparated control (USC) FSa cells irradiated *in situ* with $E_d = 50$ MeV (Be) neutrons under air breathing conditions and assayed either immediately following irradiation at Texas A & M University (USC: 0 h) or six hours later at M.D. Anderson Hospital (USC: 6 h). Each curve is the average of two experiments. The ranges shown for each point represent 1 S.E.

a sterile 25 gauge needle on a 3 ml syringe through the side of the centrifuge tube at the base of the desired band. From the 2 to 3 ml of Renografin collected, a drop was removed and its refractive index was measured using a Zeiss refractometer (Grdina *et al.*, 1973). The remaining aliquot of cells was diluted 1:10 with medium 199 containing 5% serum and then centrifuged in a clinical bench-top centrifuge for seven minutes at 450 g. Each resulting pellet was resuspended in fresh medium 199 containing 5% serum and then kept in an ice bath while cell counts were made.

Lung Colony Assay

A lung colony assay was used to determine cell clonogenicity. WBI mice were injected iv with 0.5 ml of a tumour cell suspension containing a known number of tumour cells whose clonogenicity was to be measured (Grdina *et al.*, 1976). In each 0.5 ml of tumour cell suspension, there were an additional 10^6 plastic microspheres, 15 ± 5 μm in diameter, obtained from the 3M Corporation, Nuclear Products Division, Minn. Plastic microspheres were added to increase the efficiency of the lung colony assay. Each experimental group contained six mice. Thirteen days following injection, the mice were sacrificed, their lungs removed, and the lobes separated and fixed in Bouin's solution. Colonies of tumour cells appeared as white, round nodules on the surface of the yellowish lung and were counted with the naked eye.

Survival curves were constructed after determining the surviving fraction of cells at each of the doses of radiation used. The surviving fraction of cells for the irradiated tumours was determined by dividing the number of tumour nodules formed per cell injected (cloning efficiency) for cells from irradiated tumours by the cloning efficiency for cells from untreated control tumours. The standard errors of the means are presented for all surviving fractions. Survival curve parameters D_0 and n and their 95% confidence limits were computed by linear regression analysis. These calculations were made on all neutron surviving fractions at doses from 250 rad and greater and γ-ray surviving fractions at doses from 1000 rad and greater. These points were chosen because they appeared to form the linear portion of the curves. Each of the neutron survival curves was compared with that of the unseparated control (USC) survival curve obtained at M.D. Anderson Hospital (*i.e.* delay of four to six hours from time of irradiation to the sacrifice of the animals and removal of the tumours).

Slopes of the survival curves were compared by testing for parallelism using an analysis of covariance (Brownlee, 1965). Other results were statistically evaluated with the Student's t test.

Flow Microfluorometry analysis of Cellular DNA Content

The DNA content of selected FSa tumour populations separated on Renografin gradients was analysed by flow microfluorometry (FMF). Cells analysed by this method were first fixed in 70% ethanol and then stained with mithramycin (Mithracin, Chas. Pfizer and Co., Inc., New York, N.Y.), a DNA-specific fluorescent dye that preferentially forms complexes with native DNA, following the technique of Crissman and Tobey (1974) as modified by Barlogie *et al.* (1976). The staining solution contained mithramycin, 50 μg/ml, and $MgCl_2$ (7.5 mM) in 12.5% aqueous ethanol). Cellular DNA content was measured using a flow microfluorometer described by Steinkamp *et al.* (1973), utilizing a laser wave-length setting of 457 nm. All microfluorometric analyses were performed in the Physics Department at the University of Houston.

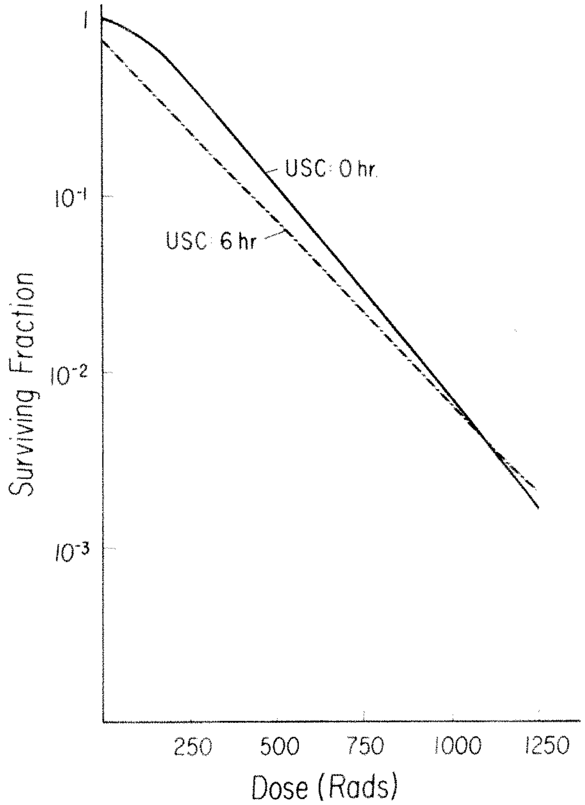

Fig. 2.

Survival curves for USC-FSa cells presented in Fig. 1 are plotted together for comparison.

The mathematical model used to fit these flow microfluorometry data is described elsewhere (Fried, 1976). Since the G_1 and G_0, and the G_2 and M-phase cells share the same DNA content and cannot be distinguished from each other, regions of the DNA-fluorescent profiles representing these cells have been designated $G_{1/0}$ and G_2+M (Barlogie *et al.*, 1976). The percentage coefficient of variation (CV), an estimate of the variabilty of the fluorescence of stained DNA in $G_{1/0}$ cells, is 100 times the standard deviation divided by the mean. The coefficient of variation of the peak representing $G_{1/0}$ tumour cells was routinely about 9%. In many cases, the data we analyzed were offset either to the right or left of the origin on the abscissa. Consequently, the observed mean of the G_2+M peak was not always positioned at twice the channel number of that observed for the mean of the $G_{1/0}$ peak. An estimate of the normal cell contamination in each of the tumour cell suspensions was made by determining the area under the $G_{1/0}$ normal peak and dividing it by the area under the total DNA histogram (*i.e.* the area under both the tumour and normal peaks).

RESULTS

Experiments were conducted to characterize the response of selected tumour populations from a murine fibrosarcoma after exposure *in situ* to fast neutrons [$E_d=50$ MeV (Be) neutrons]. Neutron irradiation appeared to have no effect on either the position or the number of cell populations banding after centrifugation in Renografin gradients. Since

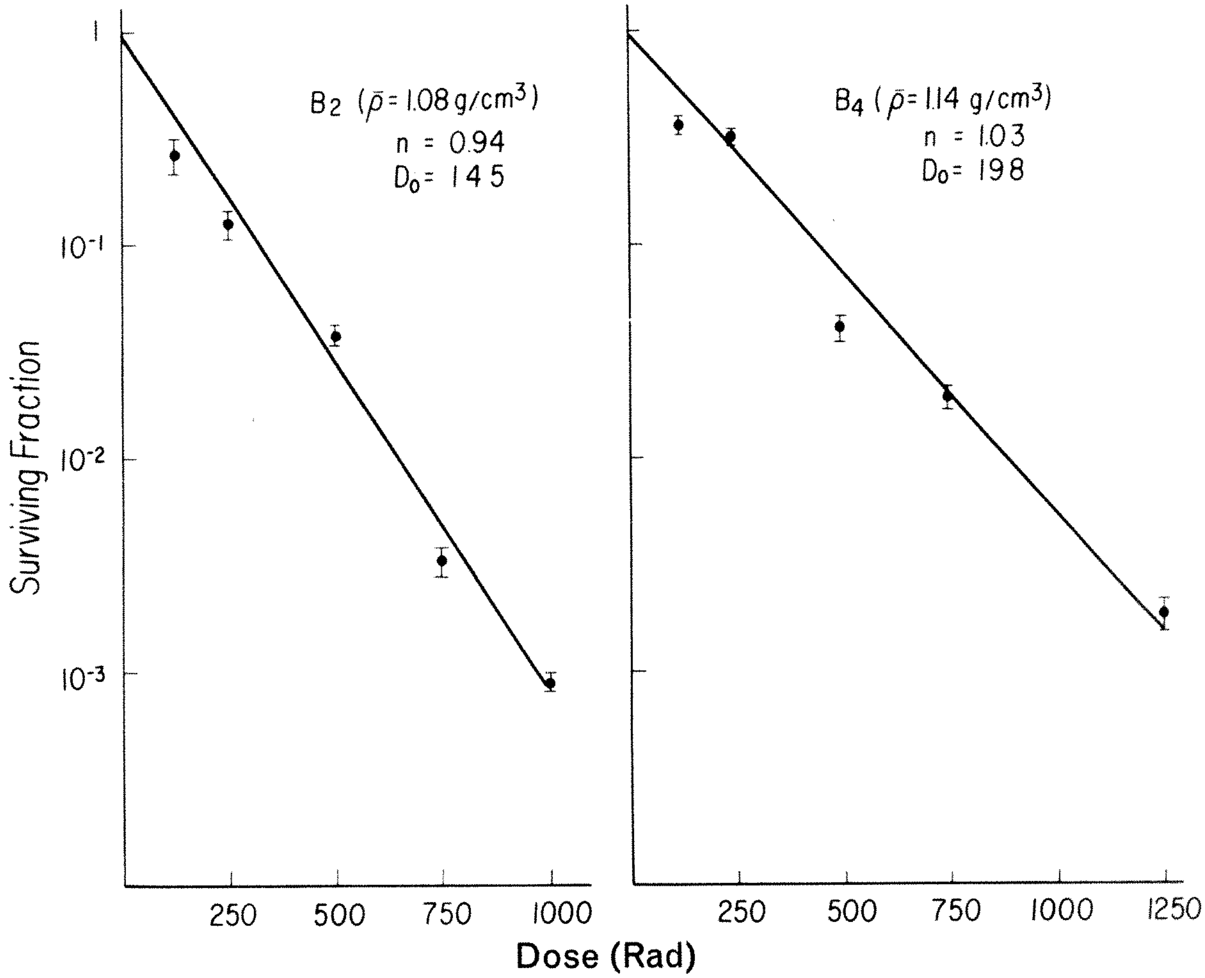

FIG. 3.

Survival curves for FSa cells separated in Renografin gradients six hours following irradiation *in situ* under air breathing conditions with $E_d=50$ MeV (Be) neutrons. Each curve is the average of two experiments. The ranges shown for each point represent 1 S.E.

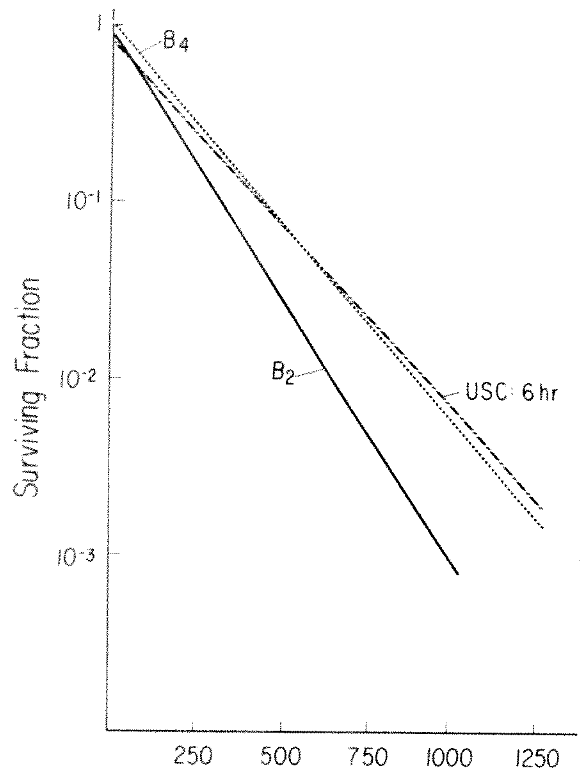

Fig. 4.

Survival curves for FSa cells presented in Fig. 1 and Fig. 3 are plotted together for comparison.

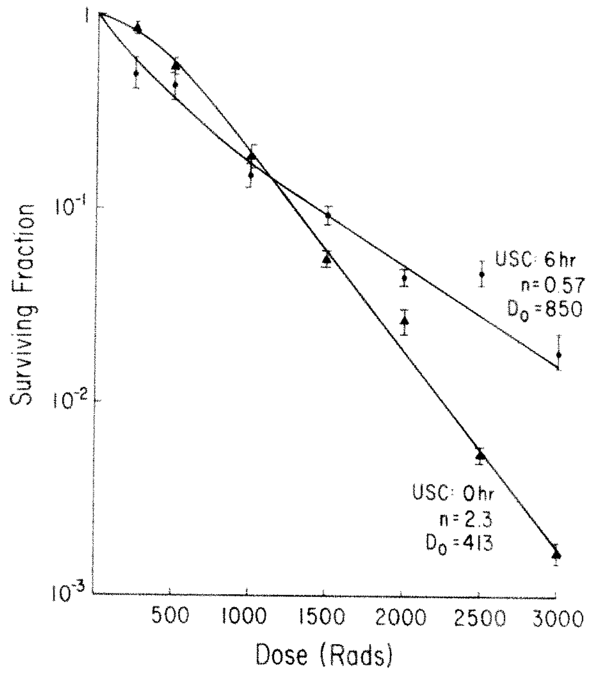

Fig. 5.

Survival curves for unseparated control FSa cells (USC) irradiated *in situ* with ^{137}Cs γ rays and assayed either immediately (USC: 0 h) or six hours following irradiation (USC: 6 h). Each curve is the average of two experiments. The ranges shown for each point represent 1 S.E.

relatively large numbers of animals and a large quantity of tumour tissue were required for the lung colony assay, the experiments were limited to unseparated (USC) cells, band 2 cells (B2), and band 4 (B4) cells. These latter two populations routinely contained about 11% and 25% respectively of the cells recovered from the gradient (Grdina *et al.*, 1976).

As described earlier, the necessary facilities were not available at Texas A & M University to conduct the cell separation experiments. Experiments were performed at the cyclotron facility, however, using unseparated cell populations. Survival curves for unseparated cells (USC) assayed immediately after irradiation at Texas A & M University (USC:0 h) or after a six-hour delay at the M.D. Anderson Hospital (USC:6 h) are presented in Fig. 1. Each survival curve is the average of two separate experiments with tumour cell survival assayed in at least 12 mice per experimental point. The cloning efficiency of unirradiated USC cells varied from 1.1 to 1.6%. No difference in cloning efficiency was apparent between cell suspensions of unirradiated tumours used as controls in the USC:0 h and the USC:6 h experiments. The values of D_0, n and associated 95% confidence limits of the USC: 0 h and USC: 6 h survival curves are: $D_0=181$ (175–187) rad, $n=1.95$ (1.67–2.28) and $D_0=202$ (196–208) rad, $n=0.75$ (0.67–0.85), respectively. The difference between the slopes of these two curves is significant ($P<0.05$). To facilitate a comparison, both curves are presented in Fig. 2.

The dose response curves of B2 and B4 cells are presented in Fig. 3. The cloning efficiency of unirradiated B2 and B4 cells varied from 1.5 to 2.0% and 1.0 to 1.2%, respectively. The B2 cells ($D_0=145$ (138–152) rad) appeared to be more sensitive to neutrons than B4 cells ($D_0=198$ (189–207) rad). These two curves along with the USC: 6 h survival curve are presented in Fig. 4 for comparison. The slopes of the B2 and USC: 6 h curves are significantly different ($P<0.01$), while those of the B4 and USC: 6 h curves are not ($P<0.1$).

The ability of fibrosarcoma cells (unseparated) to repair potentially lethal damage (PLD) after irradiation *in situ* with ^{137}Cs γ-rays was determined.

TABLE I

Repair of potentially lethal damage

Dose (rad)	Surviving fraction (%)		P	Surviving fraction ratio (6 h/0 h)
	0 h	6 h		
1000 (E_d = 50 MeV (Be) n)	0.68 ± 0.11	0.68 ± 0.05	>0.5	1.0
1250 (E_d = 50 MeV (Be) n)	0.16 ± 0.03	0.32 ± 0.04	<0.1	2.0
2500 (^{137}Cs-γ)	0.55 ± 0.04	4.84 ± 0.89	<0.001	8.8
3000 (^{137}Cs-γ)	0.16 ± 0.02	1.84 ± 0.20	<0.001	11.5

*Mean ± S.E.

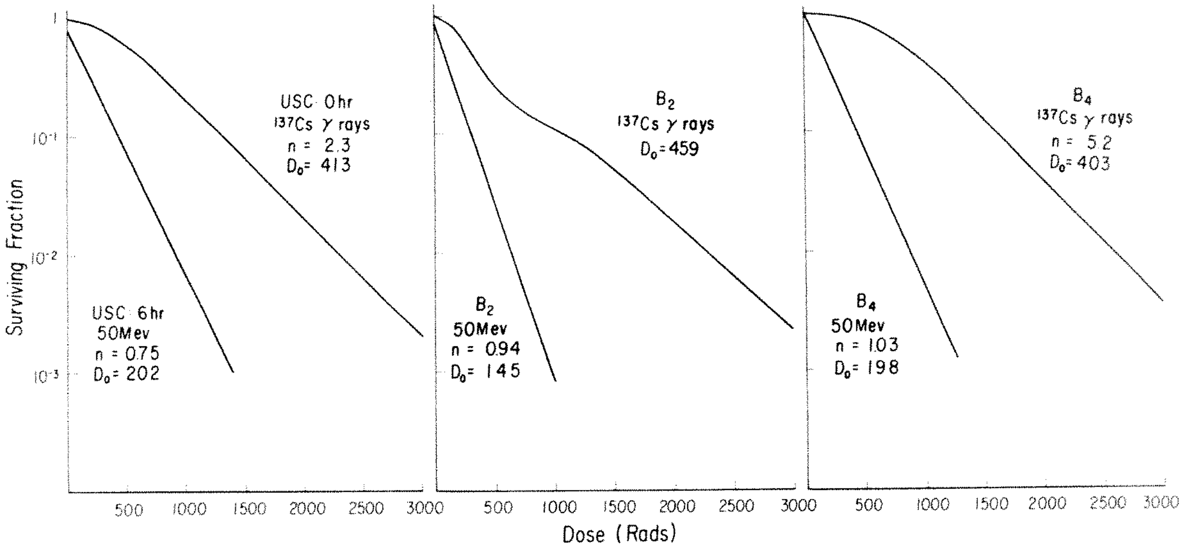

Fig. 6.

Survival curves for FSa cells (USC, band 2 and band 4) irradiated *in situ* with either ^{137}Cs γ rays or $E_d = 50$ MeV (Be) neutrons.

Tumour bearing mice were either sacrificed immediately following irradiation of the tumours (USC: 0 h) or after a 6 h delay (USC: 6 h). The two γ-ray survival curves are presented in Fig. 5 for comparison. At low doses of γ radiation fibrosarcoma cells appear to be more radiosensitive if survival analysis is delayed for six hours following exposure. A similar result is also observed following neutron irradiation (see Fig. 1, 125 rad point). Since the ability to repair potentially lethal damage is expressed by viable cells existing under relatively adverse environmental conditions, the proportion of these cells comprising the surviving population should be relatively greater following the larger doses of radiation. The divergence of the terminal portion of the survival curve at 6 h delay from that at 0 h reflects this phenomenon: USC: 0 h, $D_0 = 413$ (375–460) rad $n = 2.3$ (1.2–4.3) and USC: 6 h, $D_0 = 850$ (713–1053) rad, $n = 0.57$ (0.47–0.70) (see Fig. 5). To better compare the ability of fibrosarcoma cells to repair potentially lethal damage following irradiation with neutrons and γ-rays the surviving fractions of these cells at the relatively larger doses (less than 1% survivors) were used. The results are presented in Table I. Very little, if any, repair of potentially lethal damage occurred following neutron irradiation. Differences in surviving fractions at 0 and 6 hours after neutron exposure were not found to be significant ($P > 0.5$ and $P < 0.1$ for doses of 1000 and 1250 rads respectively).

Because of the lack of ability of USC-FSa cells to repair PLD following fast neutron irradiation, the relative biological effectiveness (RBE) for $E_d = 50$ MeV (Be) neutrons and ^{137}Cs γ rays was determined by comparing the dose of γ rays required to produce a given cellular survival (tumour-bearing mice sacrificed immediately after irradiation) to the neutron dose required to produce the same level of survival

TABLE II

RBE values for E_d=50MeV (Be) neutrons vs. ^{137}Cs γ-rays for killing FSa cells

Surviving fraction (%)	USC: 0 h*	USC: 6 hr†	B_2†	B_4†
10	2.5	3.1	3.4	3.7
1	2.4	2.5	3.5	2.9
0.1	2.4	2.4	3.5	2.7

*Cell survival assayed immediately after neutron irradiation at Texas A & M University.

†Cell survival assayed approximately six hours after neutron irradiation at the M.D. Anderson Hospital.

(tumour-bearing mice sacrificed immediately or four to six hours after irradiation). The RBE values, calculated from the survival curves in Fig. 6 are presented in Table II.

Cell cycle parameters of FSa tumours were determined using flow microfluorometry. Presented in Fig. 7 are DNA profiles of a normal spleen cell suspension, an FSa suspension, and suspensions containing an admixture of FSa cells and spleen cells in ratios of 10 to 1 and 1 to 1, respectively. The DNA profiles of the FSa suspensions consist of a peak representing normal cells in the $G_{1/0}$ phase of growth and peaks representing $G_{1/0}$ and G_2+M tumour cells located at channel numbers about 2× and 4× larger respectively. While it is uncertain as to the relative proportion of normal cells in the S and G_2+M phases contaminating the tumour suspension (*i.e.* fluorescence from these cells would be at the same channel numbers as those of G_1 tumour cells), an approximation to the relative number of normal cells present in each tumour suspension can be made by simply integrating the area under the G_1 normal peak and dividing it by the area under the entire profile.

Representative DNA profiles of USC, B2 and B4 populations, either unirradiated or six hours after irradiation with 500 rad of fast neutrons, are presented in Fig. 8. The B4 population in these experiments appears to contain the largest concentration of normal cells. Tumour cells in each of the three populations (USC, B2 and B4) are distributed throughout the cell cycle. While no correlation between cell cycle parameters and density of the cells is apparent the B2 population does contain the

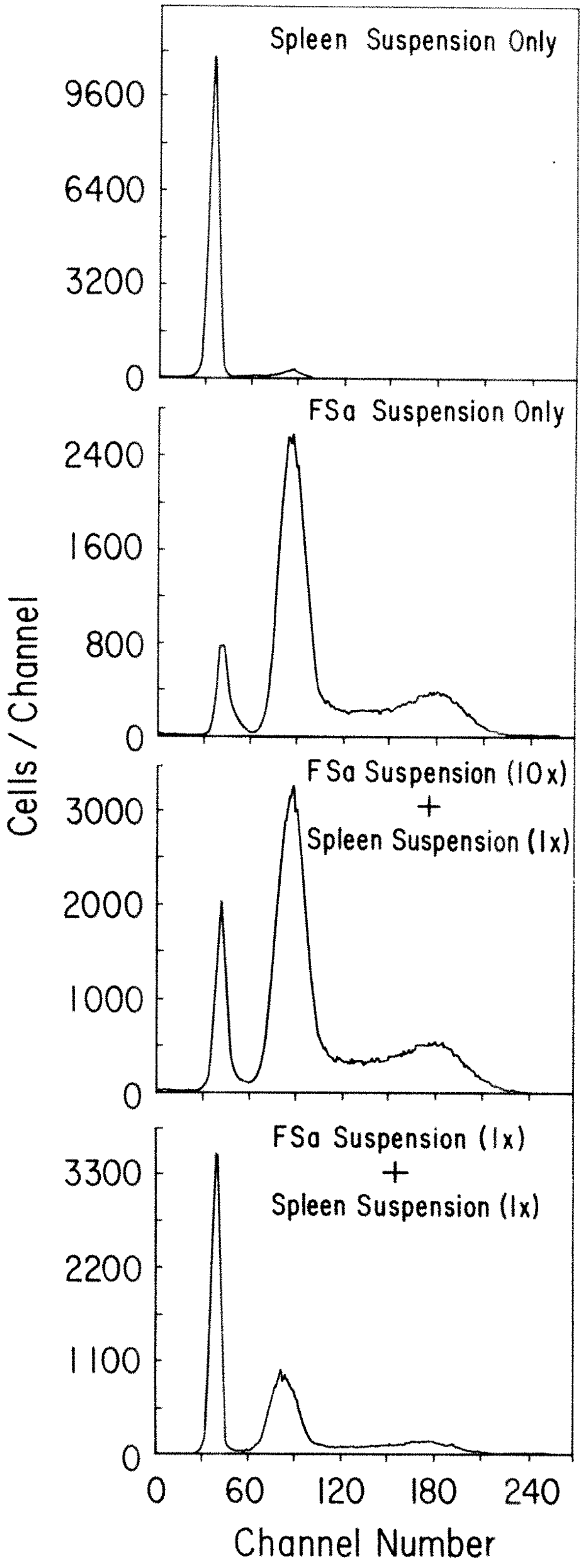

Fig. 7.

Distributions of DNA content using flow microfluorometry analysis of normal diploid spleen cells and heteroploid (USC-FSa cells) measured either alone or in combination with each other.

largest proportion of G_{10} cells. Regardless of the initial composition of the USC, B2 and B4 populations with respect to cell cycle parameters, increased numbers of cells in each of these populations appeared to be blocked in the G_2+M phase six hours following irradiation (*i.e.* USC, 19 vs. 30%; B2, 12 vs. 19%: and B4, 16 vs. 21%).

DISCUSSION

By employing separation procedures designed to exploit differences in the density of cells, at least five populations, each differing in clonogenic ability and sensitivity to ionizing radiation, can be separated from a murine fibrosarcoma (Grdina *et al.*, 1975). Two of these populations, B2 and B4 banding at densities of 1.08 and 1.14, respectively, were selected for additional study because each was homogenous with respect to cell size and morphology, and each was relatively free of cellular debris and dead cells (Grdina *et al.*, 1974a). No correlation was found between the density at which the cells banded and their relative position in the cell cycle. This is in agreement with our previous report that tumour cells involved in DNA synthesis are distributed throughout the density range used in the gradients (Grdina *et al.*, 1974a). Density invariance of cells throughout the cell cycle has also been reported for cultured cells such as Chinese Hamster and HeLa (Anderson *et al.*, 1970; Wolff and Pertoft, 1972). The clonogenic ability of cells, however, is related to density. Enriched populations of clonogenic cells are routinely recovered at the lighter density regions of gradients when complex cell systems such as solid tumours *in vivo* (Pertoft, 1970; Grdina *et al.*, 1975) and cultured cells grown to plateau phase *in vitro* (Grdina *et al.*, 1974b) are separated.

Along with characterizing the cell cycle parameters of the separated FSa populations, the method of flow microfluorometry was used to estimate the relative proportion of normal diploid cells present in each of the suspensions containing heteroploid tumour cells. These values routinely ranged from 5 to

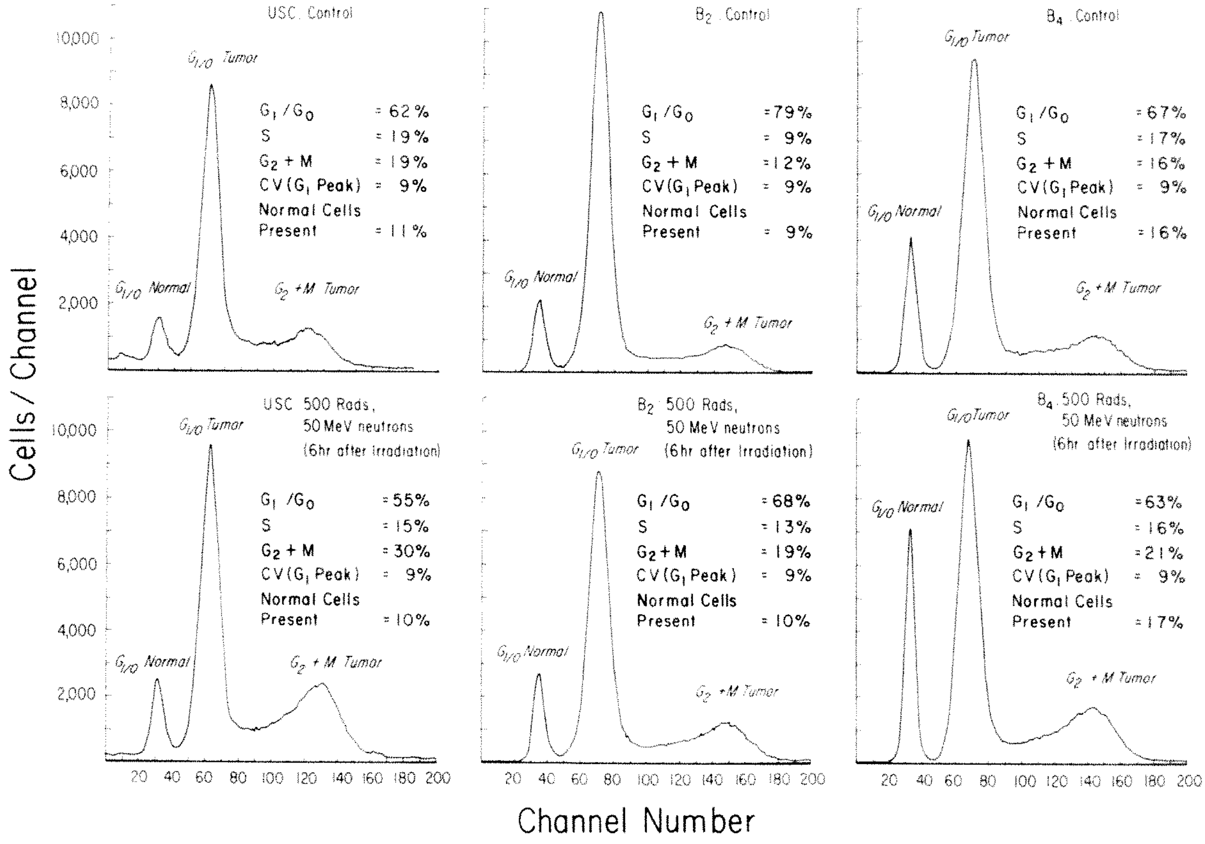

FIG. 8.

Distributions of DNA content using flow microfluorometry analysis of FSa cells (USC, B2, and B4) either before or six hours following irradiation *in situ* with 500 rad of $E_d = 50$ MeV (Be) neutrons.

15% in the tumour cell suspensions used in this study. The normal cells are probably derived from stroma, inflammatory infiltrate and vascular tissue which can be excised along with the tumour material. Using phase contrast microscopy, only the small lymphocytes could readily be identified, and these cells accounted for 4 to 8% of the total cell count. The effect of neutron irradiation on the age distribution of the various populations was determined by comparing the DNA profiles of the unirradiated controls with those from populations irradiated with fast neutrons. Irradiation induced a block in the (G_2+M) phase which was evident in each of the three populations six hours following irradiation. Similar results using flow microfluorometry were reported for EMT-6 cells five hours after irradiation with X rays under *in vitro* conditions in air (Kal *et al.*, 1975).

As described earlier, the separation of FSa cells was delayed from four to six hours following irradiation *in situ* with $E_d=50$ MeV(Be) neutrons. Since only USC-FSa cells could be assayed immediately for clonogenicity, experiments were performed to determine whether these cells could repair potentially lethal damage following neutron and γ-ray irradiation. Dose response curves were constructed and compared for cells excised immediately (USC: 0 h) or six hours after (USC: 6 h) irradiation. Cells allowed to remain *in situ* for six hours were found to have responded more to radiation at low doses than those which were excised and assayed immediately (see Figs. 1 and 5). Differences in the expression of radiation damage as related to post environmental conditions have also been reported concerning the determination of oxygen enhancement ratios (OER) for tumour growth and cell survival (McNally, 1973). The difference in OER for cell killing and tumour growth delay, 2.5 and 3.0 respectively, was attributed to differences between the types of damage expressed when cells are left *in situ* as compared to when they are removed immediately. One possible explanation is that a proportion of the hypoxic cells which survived the radiation would die from the adverse environmental conditions if allowed to remain *in situ* (McNally, 1975). These cells are, presumably, rescued from this fate if they are removed and assayed immediately. This latter procedure would give rise to larger surviving fractions. It is also possible that radiation damage may become "fixed" in a certain fraction of cells if they are allowed to remain *in situ* following exposure. These cells might then be rescued from death if they are excised immediately and thus allowed to repair this damage under a new set of environmental conditions. While this phenomenon appears to be unrelated to the quality of radiation, (*i.e.* high or low LET) the same is not true concerning the ability of the cells left *in situ* to repair potentially lethal damage. The repair of potentially lethal damage is defined and measured operationally as the increase in the surviving fraction of cells following a relatively large single dose of radiation, as a function of the time they are maintained under various post-irradiation environmental conditions (*i.e.* the increase in surviving fraction as related to the increased time cells remain *in situ* prior to their removal for the lung colony assay). At the higher doses (*i.e.* 2500 and 3000 rad), the relative number of radioresistant cells capable of repairing potentially lethal damage should increase. This was clearly evident following γ-ray irradiation of FSa cells (see Fig. 5). This phenomenon has been demonstrated in solid tumours following irradiation with X rays (Hahn *et al.*, 1974; Urano *et al.*, 1976). The maximum effect was measured for the largest dose given, 3000 rad. At this dose the surviving fraction of the FSa cells left *in situ* was 11 times greater than that found for cells excised immediately. In another tumour system, NR-S1 cells irradiated and held *in situ* for six hours yielded similar results, *i.e.* a tenfold increase in the fraction of survivors exposed to 3000 rad (Urano *et al.*, 1976). In contrast, FSa cells, at these levels of survival, were unable to repair potentially lethal damage following neutron irradiation (see Table I). The inability of tumour cells to repair potentially lethal damage following neutron irradiation has also been reported for the Lewis lung carcinoma (Shipley *et al.*, 1975) and Chinese hamster cells (Hall *et al.*, 1976).

By comparing the values of D_0 from survival curves of the two separated cell populations, the B2 ($D_0=145$ rad) appears to be more sensitive than the B4 ($D_0=198$ rad) to irradiation with fast neutrons. This is consistent with an earlier report describing the relative radiation response of these cells (B2, $D_0=143$ rad; B4, $D_0=193$ rad) to low LET irradiation under *in vitro* conditions in air (Grdina *et al.*, 1975). The relative radiosensitivity of B2 cells was also observed following irradiation *in situ* with ^{137}Cs γ rays (Grdina *et al.*, 1976). The B2 population appeared to consist of a large fraction of sensitive along with some radioresistant cells (*i.e.* a biphasic survival curve) while the B4 population contained relatively radioresistant cells which were probably chronically hypoxic at the time of irradiation.

RBE values were calculated by comparing the doses of fast neutrons and ^{137}Cs γ rays to achieve the same levels of survival. These values are generally high for a single dose of radiation if either (a) a significant difference in the accumulation of sublethal damage exists (*i.e.* at low doses) or (b) the response of the hypoxic cells is predominant (*i.e.* at high doses) (Denekamp, 1974; Barendsen, 1974). The larger values of RBE calculated for the B4 as compared to USC population are due to the enhanced concentration of radioresistant (hypoxic) cells in the former (Grdina *et al.*, 1976). Large values of RBE are also calculated for the B2 population. As shown in Fig. 6 where the γ ray survival curves previously determined at 0 hours after irradiation (Grdina *et al.*, 1976) are compared with the neutron curves determined six hours after irradiation, the levels of survival chosen to determine the RBE are on the portion of the γ ray curve describing the response of the more resistant fraction of cells (*i.e.* hypoxic). This, coupled with the radiosensitivity of these cells to fast neutrons, is the cause of the relatively large values of RBE.

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Hyperthermic sensitization of mouse intestine to damage by X rays: the effect of sequence and temporal separation of the two treatments

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ABSTRACT

Adult mice were irradiated with between 7 and 15 Gy of X rays to the abdomen either before or after immersion of the lower half of the body in water at various temperatures. The thermal enhancement of X-irradiation damage to the intestine was estimated using survival at five days as the endpoint. Thermal enhancement ratios (defined as the ratio between the dose of X rays and the dose of X rays plus heat to produce the same level of damage) were calculated at the 50% survival level. If only a few minutes separated the application of heat and irradiation, the values obtained were similar to those reported for other normal tissues. There was only a slight dependence on the sequence of the two treatments. As the time interval between the two treatments was increased the effect of heat was reduced and a normal irradiation response was obtained when the separation was greater than about four hours. The results are compared with those for other normal tissues and tumours and the relevance of these findings in the design of optimal therapeutic schedules of combined heat and X rays is discussed.

It is now well established that hyperthermia is able to potentiate the effects of X irradiation on cells (Ben-Hur *et al.*, 1974; Gerweck *et al.*, 1975; Robinson and Wizenberg, 1974), tumour pieces *in vitro* (Rohdenberg and Prime, 1921), tumours *in vivo* (Crile, 1963; Selawry *et al.*, 1958; Thrall *et al.*, 1975) and normal tissues (Robinson *et al.*, 1974; Stewart and Denekamp, 1977; Field *et al.*, 1977). It is also apparent that the extent of hyperthermic sensitization depends on the particular combination of the two treatments with regard to sequence and interval between them (Dewey *et al.*, 1977). A useful approach to the treatment of cancer with combined heat and X rays may therefore be to study these temporal relationships in both tumours and normal tissues in order to try to find optimum treatment regimes. The present work is an investigation of the extent to which hyperthermia enhances X-ray damage to the small intestine of mice and a study of the effects of sequence and time interval, for comparison with data for other normal tissues and tumours. Irradiation of mouse intestine may cause death after four to five days, due to the action of proteolytic enzymes and the loss of water and electrolyte following damage to the epithelial lining (Quastler, 1956). Survival at five days was the endpoint used in our investigations.

METHODS

Female CFLP mice (10–12 weeks old) were anaesthetized using sodium pentobarbitone at 0.07 mg/g body weight. All X ray and heat treatments were carried out under anaesthesia. Where irradiation was given immediately after heating a small additional dose of anaesthetic was given. The whole of the abdomen was irradiated using 250 kV X rays, HVL 1.2 mm Cu, at a dose rate of 1.8 Gy/min. The rest of the animal was shielded. Eighteen mice were used for each data point. Hyperthermia was achieved by immersion of the lower body up to the xiphisternum in a thermostatically controlled water bath (accurate to 0.05°C). Transfer of mice between heating and irradiation took two or three minutes. Intraperitoneal temperature was monitored using fine thermocouples which were accurate to 0.1°C and had been calibrated against a mercury-in-glass thermometer. The temperature stabilized at 0.2–0.4°C above the temperature of the water bath after approximately ten minutes of immersion. On removing mice from the water bath, intraperitoneal temperature fell rapidly. Figure 1 shows rectal and intraperitoneal temperatures of a mouse during and after immersion of the lower body in water at 41.5°C, compared with the temperature of an unheated but anaesthetized mouse. Heating times were taken from the time at which the temperature of the mouse had stabilized to the time of removal from the water bath.

As intraperitoneal temperature was increased above 41.8°C the tolerance of the mice to hyperthermia fell and survival was reduced, *e.g.* 50% death occurred within six hours after heating at 42.3°C for 60 minutes. At temperatures above 42.8°C mice died during heating, *e.g.* the mean survival time at 43.0°C was approximately 40 minutes. Injection of 0.5 ml glucose-saline (5%–0.9%) into the tail vein after treatment improved the probability of survival for temperatures up to 42°C but above this the injection had no beneficial effect. Mice which died within six hours after heating were excluded from the experiment.

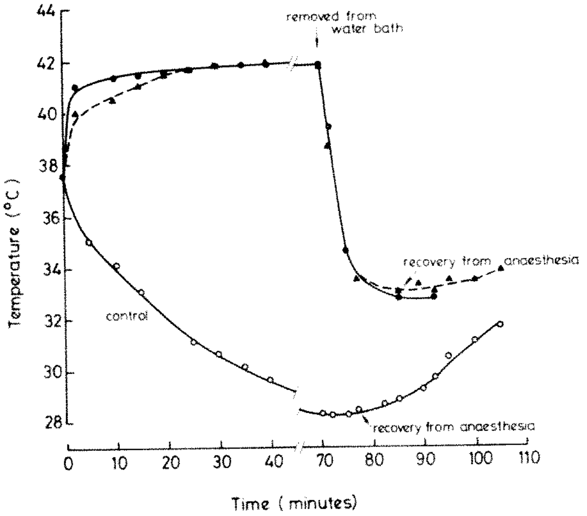

FIG. 1.

Mouse temperature during and after lower body heating compared with that of an unheated, anaesthetized control. Heating was begun at time zero, which was approximately one minute after full anaesthesia had been achieved. Temperatures were monitored using thermocouples and are intraperitoneal, ○, ●; or rectal, ▲. Water bath temperature was 41.5°C and heating was for 70 minutes. The data shown are from a single experiment but are typical.

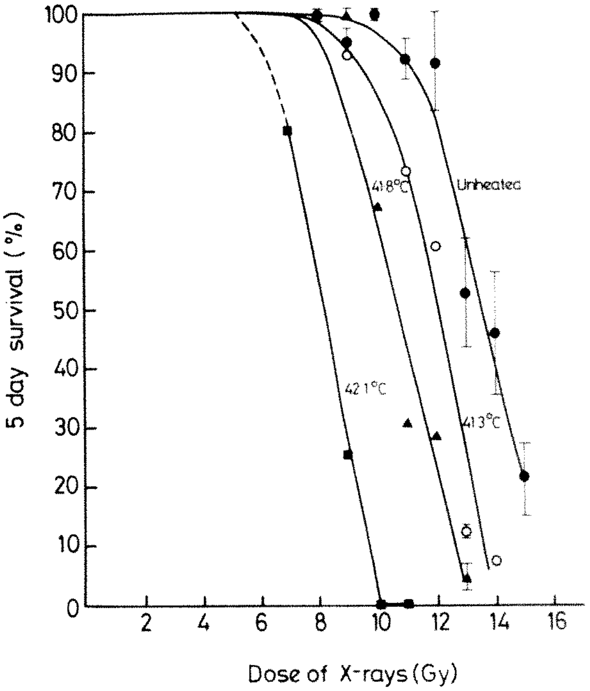

FIG. 2.

Effect of hyperthermia on the death of mice due to intestinal damage after irradiation. Immediately after irradiation mice were treated for 60 minutes at the temperatures shown. Intraperitoneal temperatures are given. Eighteen mice were used for each treatment. Mean values from several experiments are presented. The bars represent standard errors.

TABLE I

THERMAL ENHANCEMENT RATIOS

Intraperitoneal temperature, (°C)	LD 50/5 days (Gy)	TER
Untreated (31–34°)	13.50	1.00
37.0	13.50	1.00
41.3	12.00	1.13
41.8	10.70	1.26
42.1	8.20	1.65

RESULTS

Death due to mucosal injury did not occur after hyperthermia alone, and sections of the intestine appeared to be histologically normal. Death following irradiation plus heat had an identical time course to that following X rays alone, and the histological pattern of mucosal injury was similar. Thus thermal enhancement ratios could be calculated from dose-effect curves. The thermal enhancement ratio (or TER) is defined as the dose of X rays alone divided by the dose of X rays in combination with heating which produces the same level of damage (Robinson *et al.*, 1974). Fifty percent survival at five days was taken as the reference level of injury.

Figure 2 shows dose-effect curves for survival at five days after irradiation and demonstrates the potentiating effects of 60 minutes of hyperthermic treatment at various temperatures. Hyperthermia was given two to three minutes after the completion of irradiation. Thermal enhancement ratios (TER) were calculated from the curves of Fig. 2 and are given in Table I. No potentiating effect was obtained for 37°C heating.

In a second series of experiments, the sequence of and the time between the two treatments were varied using a constant hyperthermic schedule of 41.8°C for 60 minutes. TER results are shown in Fig. 3. As can be seen, if the time interval was only a few minutes, the sequence of heat before irradiation was slightly more effective than heat following irradiation (TER 1.30 compared with 1.26). As the time interval between the two treatments was increased, the potentiating effect of heat was lost. The decay was largely independent of the sequence of treatments and the response had fallen to approximately that for X irradiation alone by five hours. However, the recovery from the potentiating effect of heat was not related to time in a simple manner. The TER had a

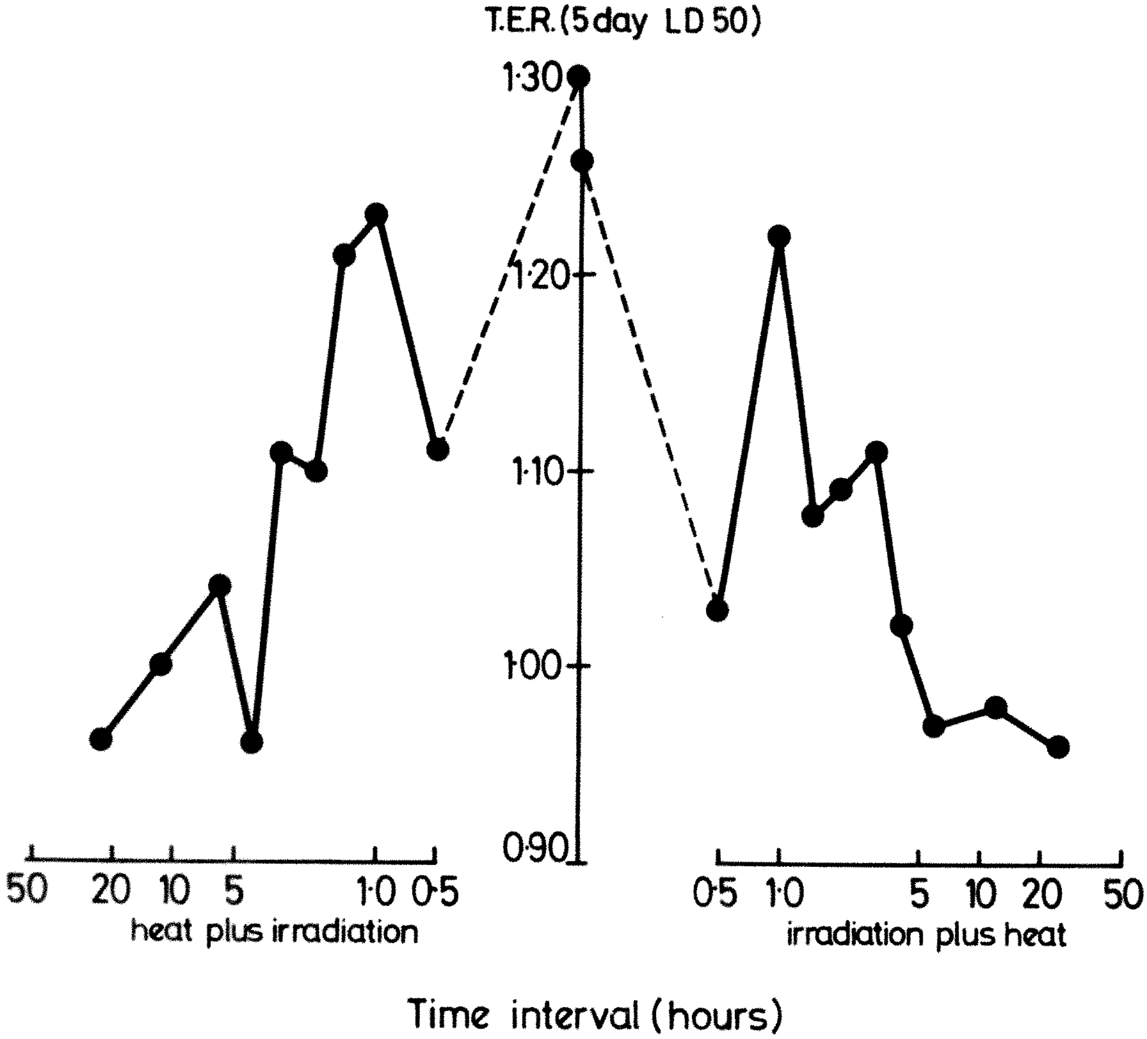

Fig. 3.

Effect of sequence and time interval on thermal enhancement of mouse death resulting from irradiation damage to intestinal mucosa. The heat treatment was 41.8°C for 60 minutes. TER values were calculated from dose effect curves (as seen in Fig. 2) using the 50% survival level. Values are taken from survival data from several experiments. The time intervals given were between the end of the first treatment and the beginning of the second.

pronounced minimum value if heat was given 0.5 hour before or after irradiation. The validity of this observation was confirmed by repeating the experiment on three separate occasions. Other fluctuations in the TER may not be significant.

Discussion

In this assay system the determination of TER for high temperatures is limited by the tolerance of the mice to the lower-body hyperthermia. The cause of this thermal death is probably a reduced blood volume and venous return, the haematocrit being increased by 10% in mice heated at 41.8°C for 60 minutes (Law and Hume, personal communication). For a 60 minute heating time, 42.0°C was the approximate limit for survival, although higher temperatures could be tolerated for shorter heating times.

For a heating time of 60 minutes there is dramatic enhancement of radiation damage above about 41°C (Table I). TER values for injury to the mouse intestinal mucosa are similar to those obtained for other normal tissues for temperatures up to 43°C (see review by Law *et al.*, 1977) although the intestine may show a greater temperature dependence after a threshold temperature is reached (Merino *et al.*, 1978). It is certainly clear that for therapy with combined heating and irradiation, when the two are given either simultaneously or not widely separated in time, the dose of X rays must be reduced to avoid excessive normal tissue injury.

The effect of the sequence of heating and irradiation on thermal enhancement has been reported for several systems, both *in vitro* and *in vivo*. The response of cells *in vitro* has been reviewed (Gerner *et al.*, 1975; Thrall *et al.*, 1976) and varying results have been reported, although the combined effect is generally reduced as the two treatments are separated by increasing time intervals. It has been postulated that variability in results is due to the different temperatures used, with higher hyperthermic "doses" being more effective if given before X rays and lower hyperthermic "doses" more effective if given post-irradiation (Dewey *et al.*, 1977).

In vivo investigations have given more consistent results than have cells *in vitro* despite the greater physiological complexity. With both normal tissues and tumours there is some variation in the TER depending on which treatment is given first. This dependence on sequence is seen in the present experiments on intestinal damage (Fig. 3), pre-irradiation heating being slightly the more effective in enhancing X-ray damage when only a few minutes separate the two treatments. This result is consistent with that found in other normal tissues (*e.g.* Thrall *et al.*, 1975; Stewart and Denekamp, 1977; Myers and Field, 1977; Law *et al.*, 1977).

With further separation of heat and irradiation there is progressive loss of interaction (Fig. 3). By four hours between the two treatments the heat has no potentiating effect on the response of the intestine to X rays. Superimposed on this loss of heat potentiation are pronounced minima at 30 minutes between the treatments regardless of which is given first. Other work on normal tissues *in vivo* has also indicated that the decay in potentiating effect of heat does not have a simple relationship with time but shows maxima and minima (Myers and Field, 1977; Law *et al.*, 1977). The reasons for this pattern of response are not clear and require further investigation, especially if heat and X rays are to be separated by intervals between a few minutes and a few hours in therapy. It is seen in Fig. 1 that the animals have fully cooled within a few minutes after heating so that fluctuations in body temperature at the time of irradiation are not a contributing factor.

The results presented here (Fig. 3) and the data of some other workers using normal tissues of rodents have been plotted in Fig. 4. In order to compare more clearly the reduction in heat sensitization for the different normal tissues and the different hyperthermic treatments, all the data have been expressed as percentage of the maximum response in each series of experiments. If heat is given post-irradiation the potentiating effect decays rapidly and is lost by about four hours in all the tissues tested. Heat given pre-irradiation remains effective over longer periods except for the intestine for which the decay in effect is similar whatever the order of the two treatments. This may reflect the comparative severity of the hyperthermic "dose" rather than inherent differences in the three tissues, a higher heat "dose" remaining effective over longer periods if given pre-irradiation.

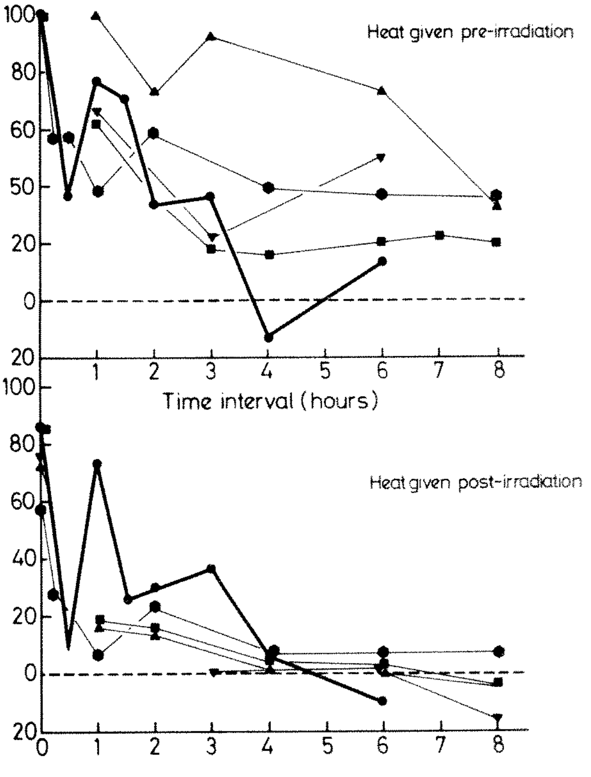

Fig. 4.

The time course of decay of heat potentiation of X-ray damage in normal tissues, for heat given either pre- or post-irradiation. Values have been normalized to percentage of the maximum response in each series of experiments and are for TER except for the baby rat cartilage data which represent the percentage stunting obtained after 10 Gy.

●	mouse intestine	41.8°C/60 min	This work.
■	mouse ear skin	42.0°C/60 min	Law *et al.*, 1977.
▲	mouse ear skin	43.0°C/60 min	
▼	mouse foot skin	42.5°C/60 min	Stewart and Denekamp, 1977.
⬢	rat cartilage	43.0°C/60 min	Myers and Field, 1977.

A possible approach in achieving a therapeutic gain appears to be in temporal separation of the two treatments, making use of different patterns of decay of heat potentiation between tumours and normal tissues as suggested by Stewart and Denekamp (1978) and supported by observations on tumours from several authors (Crile, 1963; Overgaard and Suit, 1976; Hill and Fowler, 1977; Jansen *et al.*, 1977). The aim would be to apply heat either pre- or post-irradiation with an interval such that the TER for normal tissue damage is reduced to a greater extent than for tumour control.

The results summarized in Fig. 4 support the suggestion that heating four or five hours after X rays without altering the irradiation dose might be a useful therapeutic approach. Ultimately, however, the choice of a specific combination of treatments for therapy would have to be based on an understanding of the underlying mechanisms of heat and irradiation damage and their interaction.

Conclusions

1. For a one hour heat treatment given within a few minutes before or after X rays, the potentiation of radiation damage to the intestine increases dramatically with increasing temperature above 41°C in a similar manner to that found with other tissues.

2. Potentiation of irradiation damage by heat is reduced with increasing time interval between the two treatments. By four hours after irradiation, heating does not potentiate radiation damage to the intestine or some other normal tissues. Other evidence suggests the pattern may be different for tumours.

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The therapeutic advantage of combined heat and X rays on a mouse fibrosarcoma

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ABSTRACT

The response of an experimental fibrosarcoma to combined heat and X rays has been assessed using delay in tumour regrowth. No thermal sensitization was observed for one hour of heating at 41.5°C. A thermal enhancement ratio of 1.4 to 1.5 was seen for one hour of heating at 42.5 or 43.5°C immediately after irradiation. The importance of the sequence and time interval between the two modalities was tested using a constant heat treatment of 42.5°C for one hour. Heating was most effective when given after irradiation, with little change in TER for an interval of a half to six hours. When heat preceded the irradiation the pattern was more complex, with no sensitization at half, one, and six hours, but with a significant effect at two and three hours. The degree of sensitization often depended upon the X-ray dose, being lower below X-ray doses of about 20 Gy. The therapeutic advantage of the combined treatment was assessed by comparison with previously published results for skin reactions. No therapeutic benefit was found for treatments when heat and X rays were separated by one hour or less. A therapeutic gain factor of about 1.3 was observed for heat given two to six hours after irradiation of this fibrosarcoma.

The current revival of interest in the clinical application of hyperthermia for the treatment of cancer has led to a large number of experimental studies in transplantable tumours (Crile, 1963; Overgaard and Overgaard, 1972, 1974; Muckle and Dickson, 1973; Hahn *et al.*, 1974; Robinson *et al.*, 1974; Yerushalmi and Har Kedar, 1974; Thrall *et al.*, 1975; Hill and Fowler, 1977; Marmor *et al.*, 1977).

Some tumours have been locally controlled by the application of heat alone (Overgaard and Overgaard, 1972; Crile, 1963; Marmor *et al.*, 1977), but in most studies moderate heating, in the likely clinical range of 40–43°C, caused tumour regression but not cure unless it was used in combination with some other cytotoxic agent. Combined heat and X rays have been shown to be more effective than X rays alone, and may reduce the X-ray dose needed for local control by a factor of up to five (Robinson *et al.*, 1974; Overgaard and Overgaard, 1974). However, heat also sensitizes normal tissues to radiation (Robinson *et al.*, 1974; Thrall *et al.*, 1975; Field *et al.*, 1977; Law *et al.*, 1977; Myers and Field, 1977; Morris *et al.*, 1977; Stewart and Denekamp, 1977), and in order to evaluate the possible therapeutic gain it is essential to compare the sensitization of tumours and normal tissues. Unfortunately only a few researchers have quantitatively investigated both tumour and normal tissue under standardized experimental conditions (Robinson *et al.*, 1974; Thrall *et al.*, 1975; Jansen *et al.*, 1977), and it was felt that further investigations on this topic were needed. The aim of the present study was to measure the Thermal Enhancement Ratio* for a tumour and for skin and to calculate the Therapeutic Gain Factor†. A mouse fibrosarcoma was treated with combined heat and X rays, and the tumour results were compared with our previously published skin data (Stewart and Denekamp, 1977) in order to assess the therapeutic gain. Two types of experiment are described: in the first, one hour of heating, at temperatures between 40.5 and 43.5°C, was applied immediately after X irradiation; in the second, a constant thermal treatment (42.5°C for one hour) was used at various times before or after X irradiation in order to assess the importance of the sequence and spacing of the two modalities.

MATERIALS AND METHODS

The tumour chosen was a transplantable mouse fibrosarcoma in the same inbred albino strain WHT/Ht mice used for the skin reaction experiments. The tumour arose spontaneously in 1974 and has since been maintained by serial passage; it has a volume doubling time of 2.5 to 3 days over the range of sizes used for irradiation. It is relatively radioresistant and does not shrink after subcurative doses of X rays (below 55 gray), but it does show a dose dependent delay in growth.

Tumours were implanted as approximately 1 mm cubes, subcutaneously on the ventral thorax of groups of about 100 male mice aged two to three months, under Penthrane anaesthesia. The tumours grew into solid spheroids of palpable size after about two weeks, and were selected for treatment at a mean diameter of 7–9 mm; this was usually 18 to 25 days after implantation. The mice were randomly allocated for treatment with X rays alone or with combined heat and X rays.

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*Thermal Enhancement Ratio (TER) $= \dfrac{\text{X-ray dose without heat}}{\text{X-ray dose with heat}}$ to give the same degree of injury.

†Therapeutic Gain Factor (TGF) $= \dfrac{\text{TER tumour}}{\text{TER normal tissue}}$

It is important to compare TERs over the same range of radiation doses for tumour and normal tissue.

Mice were anaesthetized with sodium pentobarbitol for heating and irradiation procedures; 60 mg/kg of anaesthetic was administered ten minutes before treatment. During a heating period of one hour an additional dose of anaesthetic (15–20 mg/kg) was usually given after 30–40 minutes. In experiments where heat and irradiation were separated by a time interval, "top up" doses of anaesthetic were given according to the condition of the mouse. For short time intervals (nought to one hour) it was usually sufficient to give an additional 15 mg/kg of anaesthetic. For longer time intervals (up to six hours) the dose was gauged for each mouse; mice which were completely awake were given 40 mg/kg and exceptionally (at six hours only) the full dose of 60 mg/kg. The tumours were immersed in a waterbath (thermostatically controlled to ±0.05°C) while the mice lay in Perspex and lead irradiation cradles on the water surface. Cool air was blown across the waterbath to reduce the humidity of the inspired air and to prevent the body temperature from rising. The heating time was always one hour. The tumours achieved a temperature 0.2°C lower than that of the water within five to 15 minutes, depending on the individual tumour. The thermostat was therefore always set at 0.2°C above the desired tumour temperature. The temperatures quoted below are *tumour* temperatures. Water and sample tumour temperatures were monitored using a Bailey thermocouple with a 29 gauge needle which had been calibrated against a standardized mercury-in-glass thermometer; these tumours were not included in the regrowth experiments.

Irradiation was with 240 kV X rays, generated at 2.6 Gy/min by a 250 kV Pantak X-ray set, filtered with 0.25 mm Cu and 1 mm Al and with a HVL of 1.3 mm Cu. Groups of four mice were irradiated simultaneously, and turned through 180 deg. half way through irradiation to minimize heterogeneity of the dose. Groups were treated with various doses of X rays alone, or with X rays combined with heat. In the first experiments one hour of heating at 41.5, 42.5, or 43.5°C was administered immediately after irradiation. In the second series a constant thermal treatment (42.5°C for one hour) was given at various times (nought to six hours) before or after irradiation.

The tumours were measured in three dimensions using vernier calipers. On the day of irradiation they were measured before immersion in water, because the hot water caused immediate swelling which lasted several hours. After irradiation tumours were measured three times a week until the average diameter exceeded 13.5 cm. The mice were then sacrificed. The geometric mean diameter of each tumour was calculated and the radiation damage was assessed from the time taken to grow 4.5 mm larger than the size at irradiation. This represents a four- to five-fold increase in tumour volume. Each dose group contained six to 15 animals.

This tumour metastasises readily to the brachial and axillary lymph nodes. Such metastases were noted but not measured, and the animals were sacrificed and excluded from the study if the metastases became large enough to be confused with the primary tumour or became a burden to the animals.

RESULTS

The delay in regrowth of the tumours relative to control animals was used as a measure of radiation and heat damage. Control unirradiated tumours took 6.7±0.3 days to grow from 7.5 to 12 mm mean diameter. One hour of heating at 42.5°C caused a

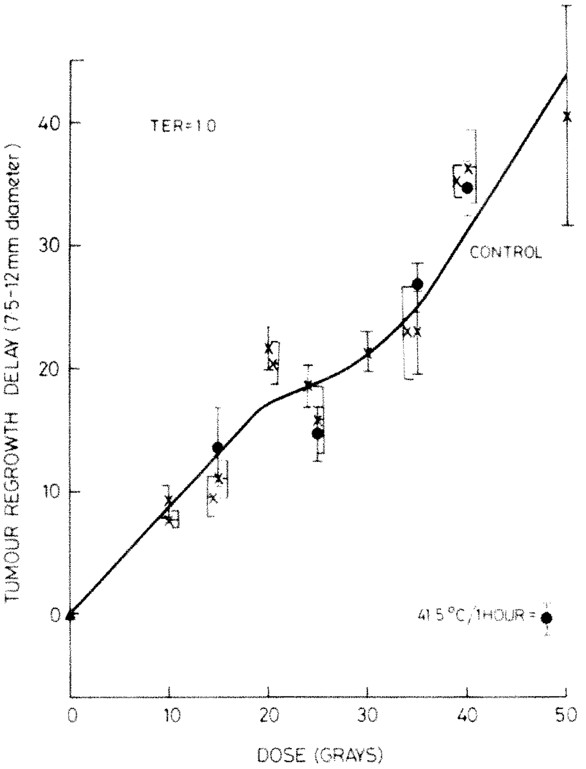

FIG. 1.

Regrowth delay as a function of X-ray dose for tumours treated with X rays alone (×) or with X rays followed immediately by one hour of heating at 41.5°C (●). There is no significant thermal sensitization. Each point represents the mean delay for six to 15 animals.

slight increase in this time to 7.6±0.9 days (*i.e.* 0.9 days delay). The regrowth time was calculated from the geometric mean diameter for each individual animal; from this a mean and standard error was computed for each dose group. This method of analysis was better than analysing the averaged growth curves for the group of tumours since tumours which regrew rapidly were sacrificed and lost from the analysis before the average curve reached the desired size. The regrowth delay values are plotted in Figs. 1–5 to give dose-effect curves. Where the error bar has an upward arrow, it indicates that one or more animals were sacrificed because of metastases before the tumour had grown the requisite 4.5 mm. Such animals were included in the analysis if the tumour was approaching the regrowth size, when the last day of measurement was used as a lower limit for its regrowth delay; hence the upward arrows.

Figure 1 shows the time required to grow from 7.5 to 12 mm for tumours treated with X rays alone or with X rays followed immediately by one hour's heating at 41.5°C. The four groups treated with heat after irradiation are not significantly different from those given X rays alone, indicating that there is no thermal sensitization at this temperature.

Figures 2 and 3 show the data for tumours heated immediately after irradiation at 42.5 or 43.5°C for one hour, together with the curve for X rays alone, reproduced from Fig. 1. A greater delay in growth was observed at each dose level for these higher temperatures, corresponding to a thermal enhancement ratio of 1.4 to 1.5 at a regrowth delay of 25 days.

Figures 4 and 5 show the data from the second series of experiments where a constant thermal treatment was used at nought to six hours before or after irradiation. In each diagram the control curve for X rays alone is reproduced from Fig. 1. When heat was applied after irradiation (Fig. 4) there was thermal sensitization at all time intervals tested, although at six hours the data are very scattered, reflecting the large animal-to-animal variability. The TER values at this time are very dependent on the X-ray dose. Except at nought hours, there was no

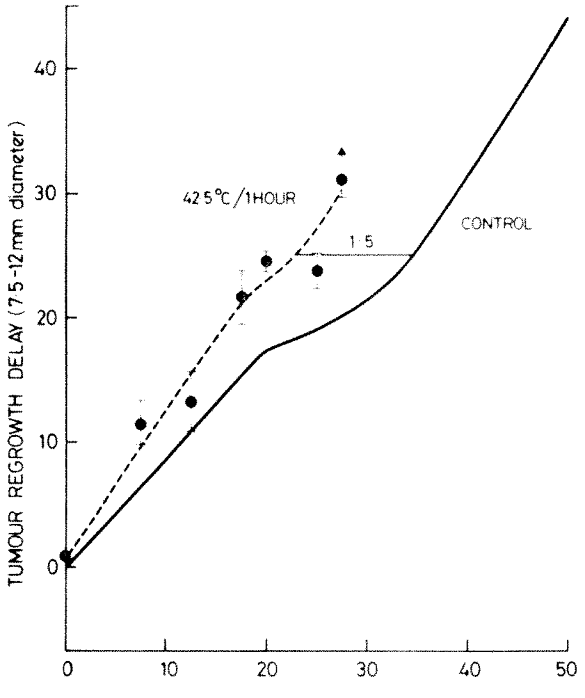

FIG. 2.

Regrowth delay as a function of X-ray dose for tumours treated with X rays followed immediately by one hour of heating at 42.5°C. The curve for tumours treated with X rays alone is reproduced from Fig. 1. The thermal enhancement ratio ranges from 1.3 to 1.7 at doses above the break point on the control curve.

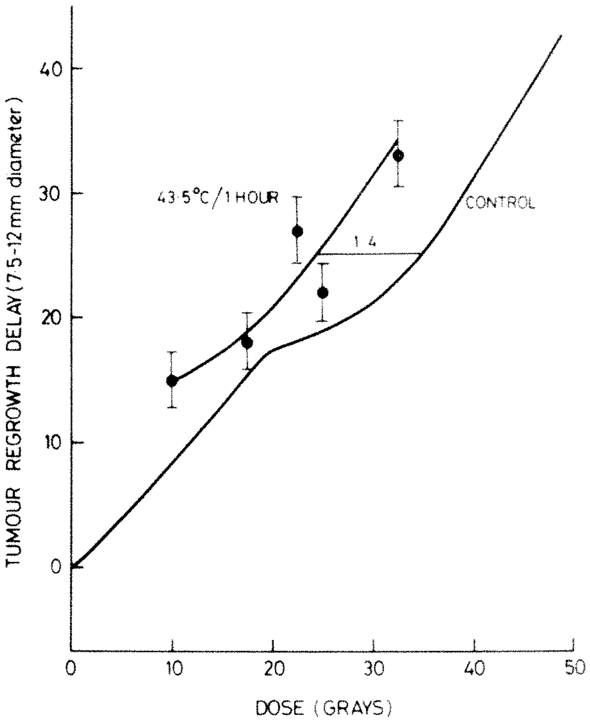

FIG. 3.

Regrowth delay for tumours treated with X rays followed by one hour of heating at 43.5°C. The curve for tumours treated with X rays alone is reproduced from Fig. 1. The TER is in the range 1.2–1.6 above the break point on the control curve.

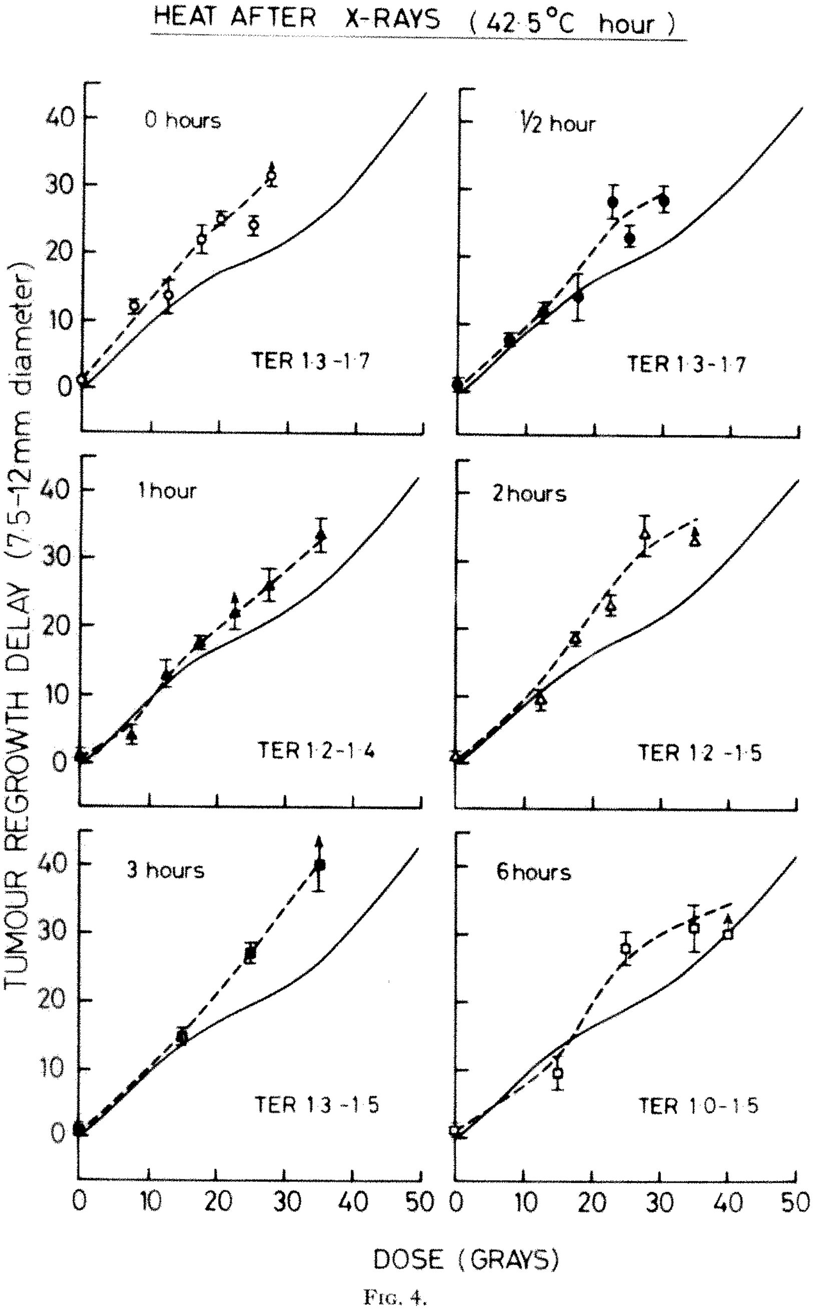

Fig. 4.

Dose response curves for tumours treated with one hour of heating at 42.5°C at various time intervals *after* X irradiation. In each panel the data points are shown for the heated tumours; the control curve for X rays only is reproduced from Fig. 1. The range of thermal enhancement ratios read from the data points relative to the control curve, above the break point at 20 Gy, is indicated. Sensitization was observed at all time intervals.

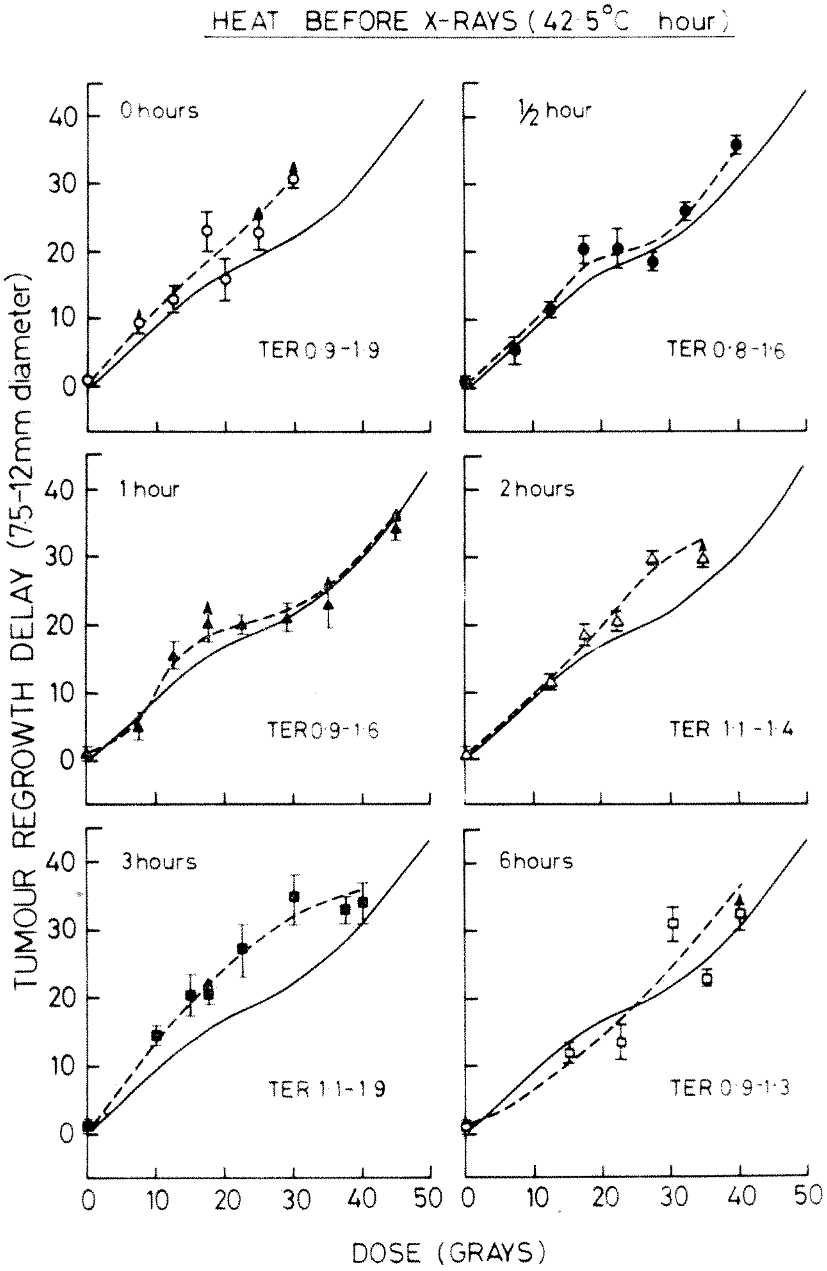

FIG. 5.

Dose response curves for tumours heated at various intervals *before* X irradiation. The control curve is reproduced from Fig. 1. The range of TER values above the break point on the control curve is indicated.

significant TER measured at doses below the "break point" on the control curve (at 20 Gy). The TER values written against each pair of curves have been derived by comparing each point for X rays plus heat with the control curve above 20 Gy.

When heat was applied immediately before irradiation thermal sensitization was also seen (TER about 1.4), but at intervals of half, one, and six hours there was little or no thermal enhancement. There was, however, some sensitization at two and three hours before irradiation, showing that when heat was applied before X rays the time interval was critical.

Discussion

In this experimental fibrosarcoma we have shown that heating sensitized the tumour to X irradiation if a temperature of 42.5°C or greater was maintained for one hour. No sensitizing effect was observed with 41.5°C for one hour. One hour of heat alone at 42.5°C caused no significant delay in this tumour (Fig. 2). The thermal enhancement ratio measured from each pair of curves varies with the size of the radiation dose, with little or no radiosensitization at low doses, below the "break point" at 20 Gy. The break point in this tumour is defined by the two separate sets of control data plotted in Fig. 1. The early sensitive phase, below 20 Gy, is unaltered by the addition of a hypoxic cell sensitizer, Misonidazole (Denekamp and Stewart, 1978), and the curve above this point breaks towards the response of fully hypoxic clamped tumours (unpublished data). This break point has been interpreted previously as representing the effect of the hypoxic subpopulation of the tumour which is more radioresistant (*e.g.* Thomlinson and Craddock, 1967; Field *et al.*, 1968; Denekamp and Harris, 1975). Increased thermal sensitization at these higher doses could represent an increased effect of heat potentiation on hypoxic cells, or on cells in nutritionally deprived or acidic regions (Hahn, 1974; Dickson and Oswald, 1976; Overgaard, 1976), since these characteristics are likely to be shared by cells at the maximum distances from capillaries. Alternatively it could represent a less effective removal of heat from these regions since heat dissipation depends upon regional blood flow. Thus the cells in the hypoxic regions may attain a slightly higher temperature than those adjacent to capillaries.

When the thermal enhancement ratios were read off the curves at different dose levels there was no effect below 20 Gy and an increasing effect with increasing X-ray dose in five of the six treatments using heat after X rays. This dependence of the extent of sensitization on the X-ray dose was less clear in the treatments where heat was applied before X rays.

Field (1977) has recently shown a variation in the TER values for skin reactions with the size of the X-ray dose. The data from his single dose studies and from fractionated experiments were analysed as a function of the dose per fraction. For small X-ray doses the TER values were low, and they increased with increasing X-ray dose, showing a similar effect for skin to that seen in the present results with tumours. Field suggested that dependence of TER on dose per fraction may actually be a demonstration of thermal tolerance in the fractionated treatments which yielded the data at small X-ray doses. However, our results indicate reduced TER with small X-ray doses for single dose experiments, so that thermal tolerance is not the explanation in our experiments. No such fractionated data are yet available for tumours but it is obviously important to demonstrate an effect at small doses of X rays if combined heat plus X rays are to be of any practical value in the clinic.

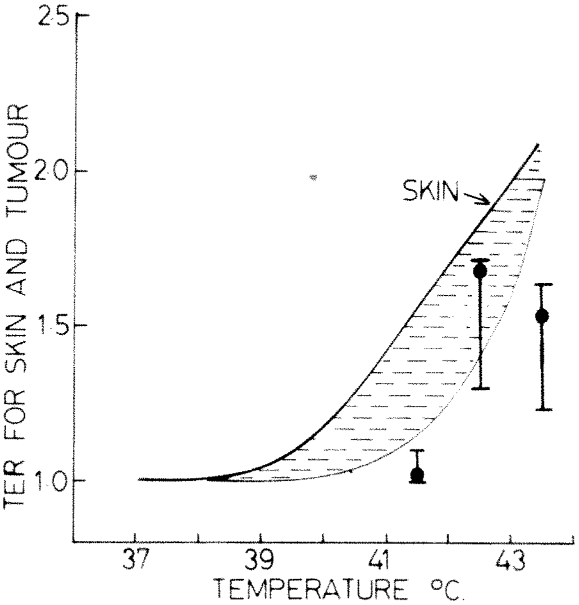

Fig. 6.

Thermal enhancement ratio (TER) as a function of temperature. The line represents the skin data published by Stewart and Denekamp (1977). The hatched area represents the range of normal tissue values reviewed by Field (1977). ● = Fibrosarcoma TER value at 20 days regrowth delay, the vertical bar being the range of TER values measured above the break point at 20 Gy.

Therapeutic gain factor

In order to assess the therapeutic potential of combined heat and irradiation, the thermal enhancement ratios for tumours have been compared with those obtained previously for skin (Stewart and Denekamp, 1977). The method of heating and of X irradiation were closely similar for the two systems. The tumour regrowth delay assay can be used over a wide range of X-ray doses and the TER values obtained have been shown to vary with dose. Therefore, for comparison with the skin reactions, thermal enhancements are read off at the level of damage produced by 27 Gy for X rays alone; this corresponds to a skin reaction of 1.5 (averaged over ten to 32 days) and to about 20 days regrowth delay for unheated X-irradiated tumours. The TER values for the fibrosarcoma are plotted in Fig. 6 as a function of temperature, together with our normal tissue data (solid line). The shaded area represents the range of normal tissue values for skin, gut and cartilage published by Field *et al.* (1977). It is clear that heat immediately after irradiation (41.5 to 43.5°C) did not produce a therapeutic advantage in this tumour relative to any of the normal tissues. The fact that the tumour values lie below the normal tissue line indicates that the combined treatment is less beneficial than X rays alone.

A similar conclusion was reached for the C_3H

TABLE I

THERMAL ENHANCEMENT RATIOS FOR TUMOURS AND NORMAL TISSUES, AND THE RESULTANT THERAPEUTIC GAIN

Authors	Heat treatment	Test system	TER	TGF
Robinson *et al.*, 1974	41°C/1 h H-X-H	C_3H mammary Ca skin (mouse foot)	1.4/1.2	1.2
	42°C/1 h H-X-H	C_3H mammary Ca skin	2.5/1.4	1.8
	42.5°C/1 h H-X-H	C_3H mammary Ca skin	3.2/1.7	1.9
	43°C/1 h H-X-H	C_3H mammary Ca skin	4.4/2.1	2.1
Thrall *et al.*, 1975	44.5°C/15 min X-H	C_3H mammary Ca skin (foot)	1.4/1.8	0.8
	44.5°C/15 min H-X	C_3H mammary Ca skin (foot)	1.3/3.5	0.4
Jansen *et al.*, 1977	43°C/1 h X-H	Mammary Ca (M8013X) skin (mouse foot)	2.1/1.8	1.2
Overgaard, J., 1977	41.5°C/1 h	Mammary Ca "C" overlying skin	1.5/*NOE	≤1.5
	42.5°C/1 h	Mammary Ca "C" overlying skin	3.5/*NOE	≤3.5
Stewart and Denekamp, 1977	41.5°C/1 h X-H	**Mouse fibrosarcoma skin (mouse foot)	1.0/1.5	0.7
	42.5°C/1 h X-H	Mouse fibrosarcoma skin	1.5/1.8	0.8
	42.5°C/1 h H-X	Mouse fibrosarcoma skin	1.4/1.7	0.8
	43.5°C/1 h X-H	Mouse fibrosarcoma skin	1.4/2.0	0.7
Hill and Fowler, 1977	42.5°C/1 h X-H	**Carcinoma NT' skin	1.4/1.8	0.8
	42.5°C/1 h H-X	**Carcinoma NT' skin	1.3/1.8	0.7
	42.5°C/1 h X-H	**Squamous Ca "D" skin	1.7/1.8	0.9
	42.5°C/1 h H-X	**Squamous Ca "D" skin	1.8/1.7	1.1

Data in this table are all from experiments where heat and radiation were given in close sequence. Heating was by immersion in water baths except Overgaard (1977) who used short wave diathermy.

*NOE = no observed effect.

**Using mouse skin data of Stewart and Denekamp (1977) for irradiation in oxygen. Values obtained for irradiation in air are slightly, but not significantly, different.

mammary carcinoma by Thrall *et al.* (1975). They demonstrated a disadvantage of X rays combined with 15 minutes of heat (44.5°C) applied immediately before or after irradiation under varying conditions of local oxygenation. When heat was applied before irradiation under clamped hypoxic conditions, or with mice breathing air or hyperbaric oxygen, the tumour was sensitized to a smaller extent than the skin, the therapeutic gain factor being 0.4 to 0.7. When heat was applied after irradiation in air or hypoxic conditions the TGF was 0.8. Only when heat was applied after irradiation in hyperbaric oxygen was there a slight therapeutic advantage (TGF 1.1). Recent work by Jansen *et al.* (1977) comparing the TER for a mouse mammary carcinoma and for mouse skin also showed a small therapeutic gain for one hour's heating immediately after irradiation (TER 1.2).

By contrast, Overgaard and Overgaard (1974) reported that the C_3H mammary carcinoma used in their laboratory was completely destroyed by modest heating combined with X rays, with little or no damage to the surrounding stroma and supporting vasculature. Robinson *et al.* (1974) also demonstrated much more thermal sensitization of their C_3H mammary tumour than of mouse skin when the irradiation was given in the middle of a one hour heating period. Thus the data for tumours given heat and X rays in close succession is conflicting, as shown in Table I. Some tumours show higher thermal enhancement ratios than normal tissues but this is not a universal finding.

The importance of the sequence and timing of heat and irradiation has previously been shown *in vitro* (Kal *et al.*, 1975), and for normal tissues (Stewart and Denekamp, 1977; Law *et al.*, 1977; Myers and Field, 1977), and we are now able to compare the effect on tumour sensitization for the same time intervals between heat and irradiation. The TER values varied markedly with the time interval when heat preceded X rays (Fig. 5) but showed little variation with time when heat was given after X irradiation (Fig. 4). When heat preceded irradiation the thermal sensitization was relatively high at nought hours (1.4); this effect was rapidly lost at half to one hour before irradiation, with an effect appearing at two to three hours and lost again by six hours. The lack of sensitization at half and one hour before irradiation may be due to the severe cooling effect on the tumour at these times. Although the mice were wiped dry after heating, the large area of ventral fur and skin available for evaporation of water caused hypothermia with a drop of the tumour temperature to 25°C. This may result in a radioprotective effect that counteracts the heat sensitization. Alternatively, the variations in sensitivity could result from thermally induced cell synchrony and consequent changes in sensitivity as the tumour cells progress around the cell cycle. Large fluctuations in thermal enhancement have also been seen for these time intervals in the skin of the mouse ear (Law *et al.*, 1977).

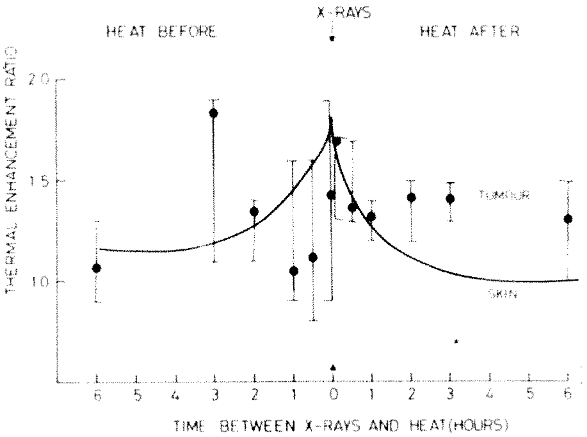

Fig. 7.

Thermal enhancement ratio as a function of the time interval between heat and X irradiation. Solid line = skin data of Stewart and Denekamp (1977). ● TER values for the fibrosarcoma at 20 days regrowth delay, *i.e.* at the same X-ray dose as used for the skin experiments. The vertical bars represent the range of values (Figs. 4 and 5).

Figure 7 summarizes the TER values for the fibrosarcoma and for mouse skin as a function of the interval between irradiation and heating. The TER values for the tumour do not exceed those for skin when the two treatments are given in close sequence, or when the heat is given at half, one, two, or six hours before irradiation. However, at three hours before irradiation, and at two to six hours after irradiation, thermal sensitization values for the tumour are higher than for skin. Thus there appear to be specific times at which a therapeutic gain would result, particularly with heat after irradiation. At other times combined heat and X rays would be significantly less effective than X rays alone. The exact timing seems to be more critical and less reliable when heat is given first rather than last.

The treatment using heat three to six hours after X rays could be particularly useful because the effect on the normal tissue is minimal at this time and no reduction in total X-ray dose would be needed to avoid excessive normal tissue damage. Other workers also report a loss of heat potentiation for normal tissues when given three hours after X rays (Field *et al.*, 1977; Law *et al.*, 1977; Myers and Field, 1977; Jansen *et al.*, 1977). These data are all restricted to single doses. It remains to be seen whether this differential loss of heat potentiation in normal tissues but not in tumours would persist for repeated fractions of heat and irradiation over similar time intervals.

There are very few other reports of the effect of varying the time interval between heat and irradiation on experimental tumours. Overgaard and Overgaard (1974) stated that the heat potentiation of X-ray damage was similar when the two modalities were applied within a 24-hour period. Hill and Fowler (1977) reported variations in the thermal enhancement observed in two different mouse tumours (a mammary carcinoma NT′ and a squamous carcinoma) as the time interval between heat and irradiation was increased. If their data are compared with thermal sensitization of normal tissues (Stewart and Denekamp, 1977; Field *et al.*, 1977) there is no therapeutic advantage for heat given immediately before or after irradiation. However, in agreement with the present data a therapeutic advantage was demonstrated in both tumours when heat was applied three to six hours after irradiation. Jansen *et al.* (1977) also demonstrated a larger therapeutic gain (1.2–1.3) with heating at four hours post-irradiation than at nought hours, although in their tumours a proportion of the effect could be attributed to direct cell killing by the heat rather than potentiation of the effect of X-rays.

Further work seems necessary to investigate and compare thermal sensitization to X rays of a variety of tumours and normal tissues. The data presented here emphasize the importance of the sequence and spacing of the heat and X rays, and also the possible importance of the size of the X-ray dose. Although this study suggests that the safest and optimum combination would be to apply heat three to six hours after irradiation, it is necessary to determine whether this would be true for repeated, fractionated, smaller doses of X rays.

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Book reviews

Chemotherapy of cancer. By Stephen K. Carter, Marie T. Bakowski and Kurt Hellmann, pp. 350, 1977. (Published by John Wiley & Sons, New York, London, Sydney, Toronto), £8·95.

Recently there have been several small books on cancer chemotherapy, most of which have been disappointing. Despite this, there is no doubt that there is a need for a short up-to-date text book which gives the non-specialist a balanced view of the theoretical basis of chemotherapy, and the specialist an up-to-date account of the drugs available, their indications for use and their side effects. For this reason, this book is particularly welcome.

Dr. Carter's reputation as an expert in his field is well known, so it is not surprising that he and his co-authors have succeeded in producing such an excellent summary of current practice. The 350 pages are divided into four sections: the first is an introduction to the strategy of cancer treatment, in which proper emphasis is laid on the increasing use of and indications for combined modality treatment. This is followed by a discussion of the basic biological concepts on cancer chemotherapy and the design of clinical trials. These topics are extremely well covered and, in particular, the section on pharmacokinetics is a model of compression without loss of necessary basic information. Discussion of clinical trials places particular emphasis on protocol design, and should be required reading for the non-specialist chemotherapist contemplating a cytotoxic drug study.

The second section deals with the anti-tumour agents currently available, the indications for their use, mechanisms of action, toxicity and modes of administration. All the major agents are listed and the section provides a sound account of conventional usage.

The third section describes the drug treatment of specific malignancies and is a good compressed account of the state of the art. Adequate numbers of references to key publications are provided.

The last section is about new approaches to cancer treatment and there is a critical account of combined modality therapy, immunotherapy and some of the new drugs that are being developed.

I think the book will appeal to a wide audience. The non-specialist will find it useful as a guide to what is available and to further reading, and for the specialist it is a convenient *aide memoire* of the drugs available and of their place in the treatment of specific tumours. It is highly recommended.

T. J. McElwain.

Ichiban (*Radiation dosimetry for the survivors of the bombings of Hiroshima and Nagasaki*) pp. viii +120, Illus. 1977. (Tennessee, US Energy Research and Development Administration) $4.75 in USA $9.50 rest of the world.

Ichiban, number one in Japanese, is the name of the project to determine the doses received by the survivors of the A-bombs. These survivors represent the largest human population exposed to ionizing radiations. Knowledge of the doses received by them would thus enable dose-response curves to be established. In view of the large use of radiation in medicine and other walks of life, an estimate of the risk based on human data is obviously of the utmost importance.

The book by Auxier—a leading member of the Ichiban project—is a fascinating review of the tremendous effort to establish the dosimetry. After ascertaining the location at the time of the explosions of a number of survivors, and working out the explosive power of the bombs, the main task was to determine the physical parameters of the radiations, *e.g.* their attenuation in passing through walls at different angles and the scatter from these walls. The scene was reconstituted in the Nevada desert, where replicas of Japanese houses were erected, and nuclear bombs exploded of the same yield and same height as in 1945. At least 4 test explosions were carried out, but the results did not agree with each other. By that time the Test Ban Treaty came into force and other methods of simulating the radiations from the bombs had to de devised. These included a pulsed fast reactor which was bodily hoisted to the top of a tower 1527 ft. high.

The irony is that a great deal of this trouble could have been avoided, if it were not for the senseless attitude of the US occupation force. A Japanese team entered Hiroshima soon after the explosion, and carried out a thorough investigation, including measurement of radiation levels, collecting samples of soil and buildings and the photographic films in shops in the city. This invaluable material, including all notebooks, was confiscated by the military, and despite a rigorous search, was never recovered.

The result of the heroic efforts of the Ichiban project was the establishment of dosimetry values known as T65D; these kerma doses serve as a basis for evaluating the absorbed doses of the survivors. The conversion of kerma into absorbed dose equivalents (Sieverts) in different tissues is still not complete. Not enough is also known about the doses received by those who entered the cities after the explosions. Thus, even from the physics angle, the saga of the Hiroshima and Nagasaki survivors is still unfinished.

J. Rotblat.

1978, *British Journal of Radiology*, *51*, 317–318

APRIL 1978

Short communications

Hypoxic cell sensitization by misonidazole *in vivo* and *in vitro*

By N. J. McNally, Ph.D., Juliana Denekamp, Ph.D., P. W. Sheldon, M.I.Biol. and I. R. Flockhart, Ph.D.

Cancer Research Campaign, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

(*Received November, 1977*)

The effect of misonidazole (Ro 07–0582, Roche Products Ltd., Welwyn Garden City, Herts.) as a radiosensitizer of hypoxic cells has been reported for several cell lines *in vitro* and for many tumour lines grown *in vivo* (Adams *et al.*, 1976a). However, there have been no direct comparisons of the effects of this drug *in vivo* and *in vitro* because of a lack of data on the intra-tumour concentration of the drug. Recently Flockhart *et al.* (1977) have developed a method to measure the concentration of unchanged misonidazole in tumours by gas-liquid chromatography. This article reports measurements of the ability of misonidazole to sensitize hypoxic cells in four different tumours to radiation as a function of its measured concentration in the tumours at the time of irradiation. These results are compared with those previously obtained for cells in culture.

The four tumours used arose spontaneously at the Gray Laboratory and have been maintained by subcutaneous passage in the substrain of origin. They are a mammary carcinoma (NT^1), a fibrosarcoma (Fib/T), an undifferentiated osteosarcoma (BS2) and an anaplastic derivation of a mammary carcinoma (MT). The details of their properties and the assay techniques have been described in detail elsewhere (Denekamp and Harris, 1975; Sheldon *et al.*, 1976; McNally *et al.*, 1978). In order to assess the radiosensitization achieved with various concentrations of misonidazole, the sensitizer enhancement ratio (SER) was measured for each tumour by determining the ratio of the dose in the absence of the drug to that in its presence to achieve a constant level of damage. For BS2 and NT^1 this was obtained from pairs of regrowth delay curves, the SER values being measured at the highest levels of growth delay, so that they most closely resemble the SER of the resistant hypoxic subpopulation of cells. For MT and Fib/T, tumours were exposed to a single dose of radiation (14 Gy for Fib/T and 50 Gy for MT) in the presence of the drug and the resulting effect compared with the effects determined from full dose-effect curves for non-drug treated animals. An equivalent radiation dose in the absence of the drug could then be obtained and an SER calculated. The assay for MT was the probability of local tumour control, and that for Fib/T was cell survival *in vitro* following treatment *in vivo*.

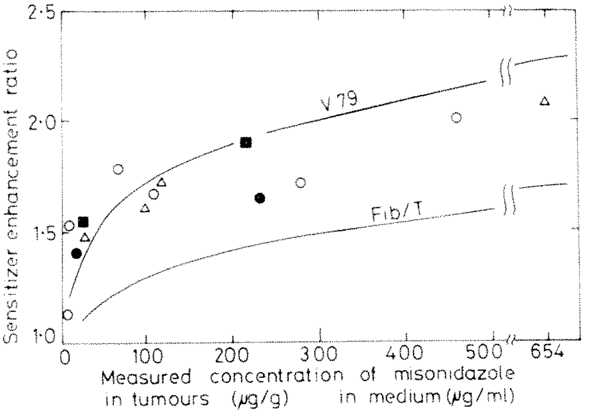

FIG. 1.

Enhancement ratios plotted as a function of the measured drug concentration in the tumour at the time of irradiation. The upper line is for V79 379A Chinese hamster cells *in vitro*, and the lower one is for Fib/T cells *in vitro*.
○ Fib/T; △ MT; ■ NT^1; ● BS2.

The figure shows these enhancement ratios for the four tumours, plotted as a function of the measured intra-tumour concentration in similar tumours sampled at the appropriate times. Two solid lines are shown to represent the sensitization seen *in vitro* with two different mammalian cell lines. The upper line is for V79 379A Chinese hamster cells (Adams *et al.*, 1976b), and the *in vivo* tumour data fall close to this line, particularly at low drug levels. The lower line represents preliminary data for cells taken from Fib/T tumours and irradiated 18 hours after they had been plated *in vitro* (McNally, unpublished). This cell line appears to show less sensitization when irradiated *in vitro* than the parent tumours assayed *in vitro* after irradiation *in vivo*. It is also sensitized less than V79 cells *in vitro*. The reason for this is not known. The figure shows that the effect of misonidazole on tumours *in vivo* is similar to that obtained for a purely hypoxic cell population *in vitro* (V79 cells) and is even greater than that obtained for another *in vitro* line.

Maximum tumour drug concentrations in mice are generally 20–50% of the peak serum levels, probably because of the short biological half-life of 1 to 1½ hours in the mouse. In man, drug concentrations in tumours usually fall in the range 50–100% of the peak serum level, because of the much longer half-life of 8–18 hours. Therefore a two- to three-fold higher tumour concentration is achieved for the same serum level in man compared with the mouse. The drug dose that can be used clinically is limited by the neurotoxic side-effects of the drug to a total dose of 12 g/m^2 in a fractionated course of treatment, with no single dose more than 4 g/m^2 (Dische *et al.*, 1977). Six equal doses of 2 g/m^2 or 50 mg/kg would give a peak plasma level in man of 60–70 µg/ml with a corresponding tumour level of 30–70 µg/g. The figure shows that this would give an enhancement ratio of 1.4 to 1.7 for large single doses of radiation, or for tumours with high hypoxic fractions. With fractionated irradiation of tumours with unknown hypoxic fractions the enhancement ratio would be smaller. However, there is every reason to expect that there will be useful enhancement in the clinical range of drug dosage.

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Book reviews

Biological effects of microwaves. By S. Barański and P. Czerski, pp. 234, illus., 1976 (Dowden, Hutchinson & Ross, Inc., Stroudsburg, Pa., USA, Chichester, John Wiley & Sons Ltd.), £9·00.

The authors of this book are both members of the International Academy of Aviation and Space Medicine in Warsaw. Each is responsible for a different aspect of the work carried out in the Academy, and between them they have produced a book dealing in considerable detail with a subject which does not figure a great deal in current scientific literature in this country. The subject is, however, one of growing concern to people engaged in a variety of activities, all of whom in one way or another may be exposed to microwave radiation to a greater or lesser degree.

The book deals first of all with the physical characteristics of microwaves and deals briefly with the basic physics of electromagnetic radiation and to some extent with its propagation. The basic interaction processes of microwaves with living systems are then described. These processes are dealt with at all levels from the molecular level up to the possibilities of what may be expected to happen in a whole organism such as an animal or a human being. Results of observations and experimental studies published in the scientific literature are drawn upon and referred to in the descriptions of biological effects.

Some idea of the scope of material covered can be obtained from the following list of topics: thermal effects, effects on the nervous system, cardiovascular effects, endocrine and metabolic effects, the reproductive system, effects on chromosomes, mitosis and cellular effects and the production of cataracts.

The symptoms of microwave over-exposure are discussed and illustrated by information collected from over 1500 workers who had experienced some sort of microwave exposure. The book concludes with a section on safe limits of exposure and discusses the prevention of health hazards.

A glance at the list of 614 references indicates that a great deal of work in this field has been done in Eastern Europe and the United States of America. A number of very minor errors of expression have crept in, presumably as a result of the translation into English but they do not detract from the intended meaning.

This is a book written by scientists for scientists, and the authors have achieved what they set out to do as stated in the last paragraph of their preface: "our principle aim was to avoid any misquotations of findings or distortion of views expressed by others and to indicate clearly where personal, subjective, and probably highly controversial opinions are given."

N. W. RAMSEY

Radiologic science: a workbook and laboratory manual. By Stewart C. Bushon, (C. V. Mosby Company; U.K. Henry Kempton), pp. 202 + xi, illus., 1977 £6·10.

This book is written for "X ray Technologists"; to a large extent it covers material in radiological physics, radiation biology and radiation protection appropriate to MSR or Part I F.R.C.R. in diagnostic radiology.

The format consists of 64 tearout worksheets and 10 laboratory experiments. Each worksheet consists of a few short comments relating to the subject matter followed by a set of exercises which consist of both multiple choice questions and those designed to test the student's understanding in depth. The experiment section provides a stated object, a discussion on the relevant principle, a suggested procedure and appropriate tables and graph paper to carry them out.

Altogether this book is an entirely welcome workbook useful to both student and teacher; the questions have been found to explore each subject tackled, with few exceptions in a very practical rather than academic way. There are certain areas where greater depth would have been desirable, *e.g.* the practical effects of X-ray equipment performance.

The manual is designed to be used with a companion textbook of the same title. Herein lies a danger, that, presented with this very attractive workbook, the student will rely upon this and group discussion, which this book will certainly stimulate, and neglect his essential background reading.

I am sure this book forms a very excellent aid to the study of its subject.

J. A. GARRETT.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *B.I.R. BULLETIN* which is distributed quarterly to all members.

THE EDINBURGH E.A.R. CONGRESS EDUCATIONAL TRUST

The Edinburgh E.A.R. Congress Educational Trust has been established following the 3rd European Congress of Radiology in order to promote the educational and research aspects of radiology. The Trust is managed by Trustees appointed by the European Association of Radiology, the British Institute of Radiology and the Royal College of Radiologists.

The endowment of the Trust amounts to approximately £45 000. It is proposed to use the Trust funds to promote the interchange of scholars, scientists and radiologists, to encourage the exchange of ideas and educational aspects relative to radiology and radiotherapy, and to further research in those fields.

Provision will be made for the granting of bursaries, scholarships, travel awards and financial assistance including supplementary grants for those involved in educational or research programmes within the member countries of the European Association of Radiology.

Consideration will also be given to financial assistance in providing or contributing towards educational training programmes, reference facilities, congresses or symposia in radiology and its allied subjects.

Application forms in English, French or German may be obtained from the Edinburgh E.A.R. Congress Educational Trust, c/o, W. & J. Burness, WS., 12 Hope Street, Edinburgh, Scotland. U.K.

RECENT ADVANCES IN HYPERTHERMIA RESEARCH

A radiobiology meeting will be held on May 11–12, 1978. Titles of papers on technical, biological or clinical aspects of the topic are invited and should be sent to Dr. S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, London W12 0HS not later than April 14, 1978.

Further information from the General Secretary, B.I.R. (01–935 6237).

B.I.R. ANNUAL CONGRESS JOINT MEETING AND SCIENTIFIC EXHIBITION 1978

The Annual Congress will include a joint meeting with the Royal College of Radiologists, the Royal Society of Medicine (Section of Radiology) and the Netherlands Radiological Societies, and will be held at the R.I.B.A., London, W.1 on April 13–14, 1978. Details from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

The "SILVANUS THOMPSON MEMORIAL LECTURE" will be delivered at this congress by Sir John Hill, Chairman U.K.A.E.A. under the title "Nuclear Power and the Environment".

SECOND CONGRESS OF THE EUROPEAN SOCIETY OF NUCLEAR MEDICINE

The Institute and other UK members of the European Society of Nuclear Medicine will be hosts to this congress to be held in London, April 17–18, 1978. The meeting will include a commercial exhibition, scientific demonstrations and technologists sessions.

Further information from the General Secretary B.I.R.

B.I.R. CONVERSAZIONE

Will be held at Northwick Park Hospital, Middlesex on May 17, 1978. Dr. Louis Kreel will arrange demonstrations and give a talk "Introducing art into radiology".

Details from the General Secretary.

HIGH DOSE RATE AFTERLOADING GYNAECOLOGICAL IRRADIATION AS AN ADJUVANT TO GYNAECOLOGICAL SURGERY: AN ASSESSMENT OF THE CATHETRON

An evening meeting will be held on May 18, 1978 at The British Institute of Radiology (Reid-Knox Hall), 32 Welbeck Street, London W1M 7PG.

Further details from the General Secretary.

BENIGN BONE DISEASE–ROLE OF RADIOISOTOPE TECHNIQUES

A joint meeting of the British Orthopaedic Association and The British Institute of Radiology, will be held on May 31, 1978 at the Middlesex Hospital Medical School, London.

WORLD FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY

To be held September 17–21, 1978. The Second International Congress of the World Federation of Nuclear Medicine and Biology will provide an international forum for the exchange of scientific information, the dissemination of knowledge, and the world-wide promotion of the discipline of nuclear medicine.

The Scientific Symposia will encompass all the activities and interests of nuclear scientists and physicians: medical and health physics; instrumentation; data analysis; radiochemistry; radioassays; *in vivo* and *in vitro* biochemical and physiological measurements; radiopharmaceuticals; functions and disorders of the cerebral, pulmonary, cardiovascular, abdominal, renal,, peripheral vascular, bone, joint endocrine, and metabolic systems.

There will be three pre-meeting courses: cardiovascular nuclear medicine; positrons, cyclotrons, and tomography; nuclear medicine in developing countries. During the meeting, there will be review teaching sessions on the state of the art in clinical nuclear medicine.

The technologist programme will include considerations of quality assurance, recruitment, education and career opportunities.

The meeting has been designed to afford maximum opportunities for exchanges of ideas and views among nuclear colleagues.

Morning activities will provide a plenary session, time for small discussion groups, and for visiting the exhibits of equipment and radiopharmaceutical manufacturers.

Afternoons will be devoted to contributed papers, poster sessions, panels and mini-symposia.

Further information from Dr. H. N. Wagner, President, WFNMB Second International Congress, 1629 K Street, N.W., Suite 700, Washington, D.C., 20006, USA.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

Forthcoming events and other notices

WORKSHOP ON THE USE OF COMPUTERIZED TOMOGRAPHIC SCANNERS IN RADIOTHERAPY

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proferred papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

Obituary

K. E. Jefferson, M.A., F.R.C.P., F.R.C.R.

Dr. Jefferson, senior radiologist at the National Heart Hospital and consultant radiologist at St. George's Hospital, died on October 23, 1977. He was 54. Educated at Oundle, Clare College, Cambridge and Guy's Hospital, he qualified in 1946. Early in his career, after obtaining the M.R.C.P. and D.C.H., he chose to specialize in radiology and following training posts at St. George's Hospital, was appointed to the consultant staff of St. George's and Brompton Hospitals in 1956. His main interest was always in the heart, so that when the new South Block at the National Heart Hospital opened in 1961, Jefferson was the obvious choice to develop the expanding field of cardiac radiology and he rapidly became internationally recognized as one of the world's leading cardiac radiologists. A great part of his success was due to his ability to integrate cardiac medicine and radiology. His teaching sessions were always well attended and as a lecturer he was outstanding. He undertook many lecture tours abroad, particularly in South America which he visited on numerous occasions and made many friends. Winner of the Barclay prize of the British Institute of Radiology in 1960 for the paper "Thoracic Aortography and Cine Radiography of the Aortic Valve", he was a member of the Thoracic and British Cardiac Societies and the British Institute of Radiology. He was also a corresponding member of several radiological societies in South America, and in 1975 was Charles Berns Lecturer and visiting professor at the Bronx-Lebanon Hospital, New York. In 1971, he delivered the National Heart Hospital St. Cyres Lecture on "The Skeleton in Heart Disease". He made many significant contributions to the literature, in particular as co-author of the book, *Clinical Cardiac Radiology*, which was the fruit of patient hours of teaching and research spread over a number of years. He presided over the X-ray department at the National Heart Hospital like a benign father, gaining not only the respect but the friendship of the staff at all levels. He was also a most successful chairman of the National Heart Hospital Medical Committee, being patient, tolerant and polite but firm when the occasion demanded.

He will be sorely missed by his many friends and colleagues, perhaps most by those to whom he gave inspiration to take up radiology as a career. A number of housemen and registrars who passed through St. George's and the National Heart Hospital will remember with respect and gratitude the kindly and charming yet expert way he would solve a clinical problem from the X-ray. His death came as a deep shock and has left a gap which will be impossible to fill. He is survived by his widow.

S. REES

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18 INTERNATIONAL EMINENT INVITED SPEAKERS
WILL BE IN JOHANNESBURG
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There will be extensive coverage on the latest trends in diagnostic radiology, with special reference to Ultrasonography and C.T. scans and also particular coverage of paediatric, gastrointestinal, and cardio-vascular fields.

There will be both separated and integrated sessions on nuclear medicine.

The international invited speakers, who will cover their respective fields are from USA, United Kingdom, France, West Germany, Australia and Israel, together with honorariums from many other countries.

For further information please contact:

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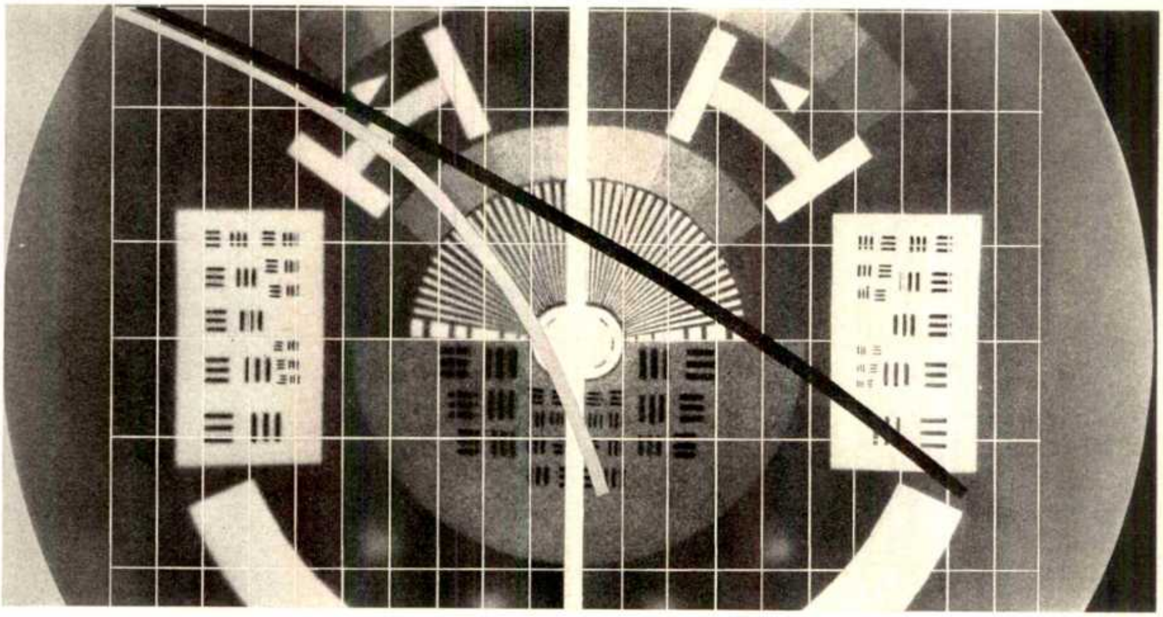

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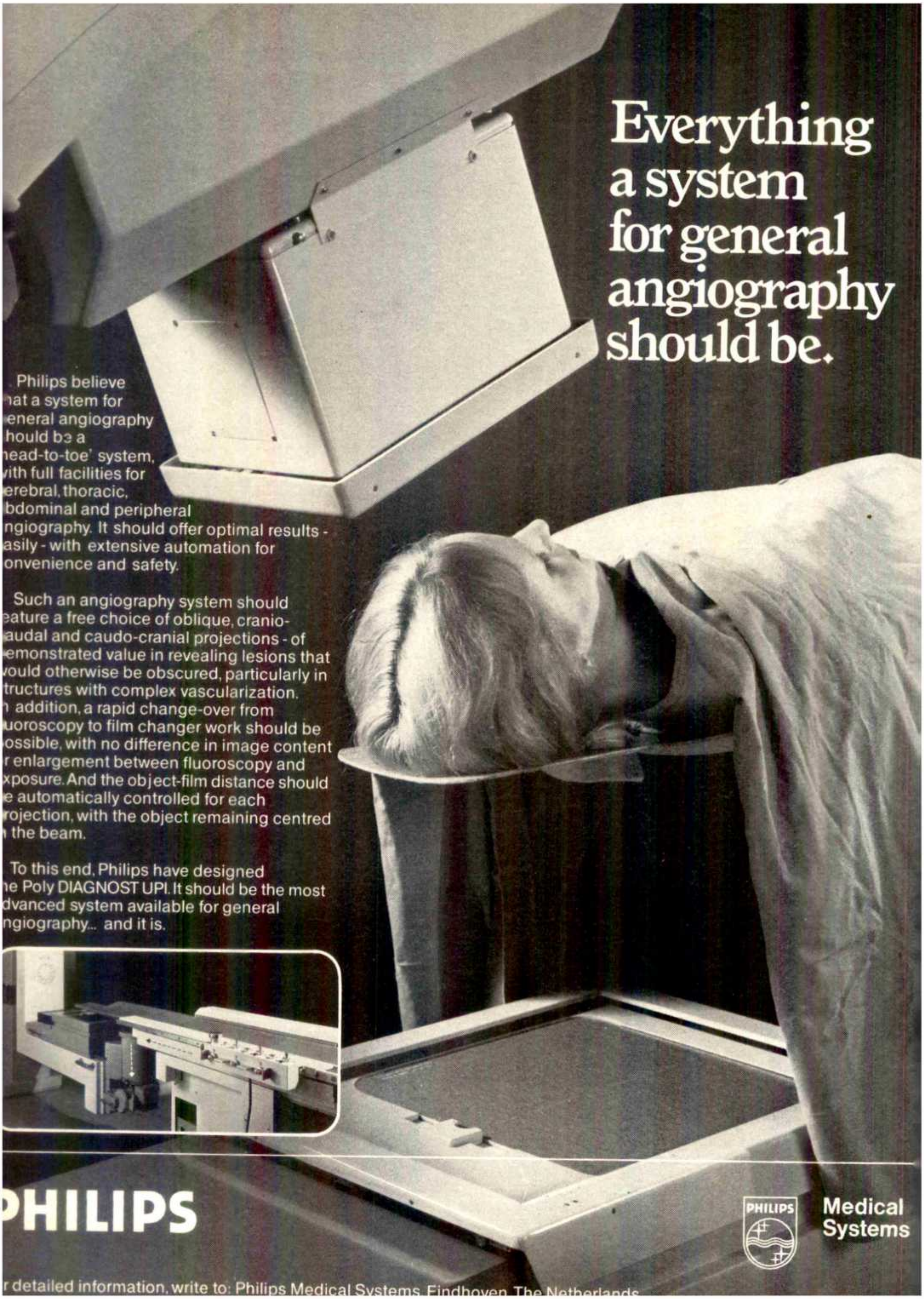

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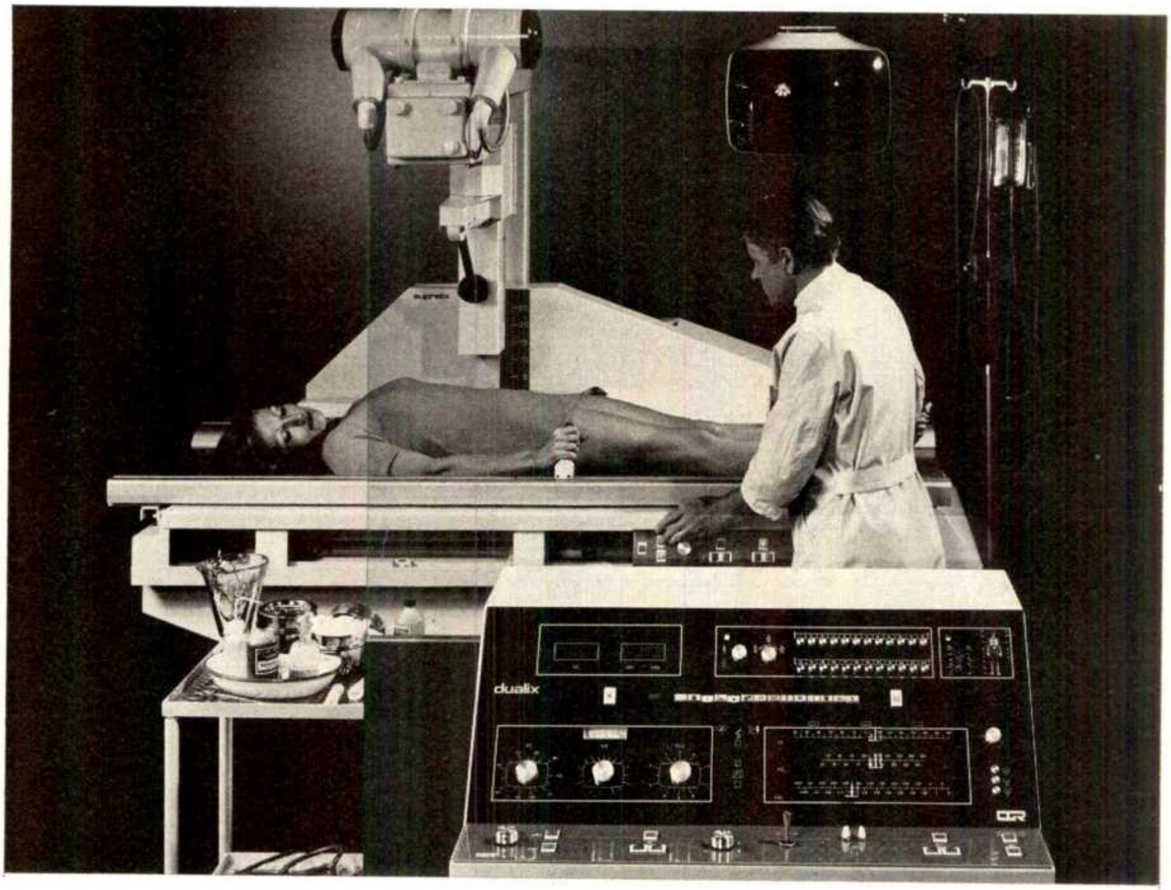

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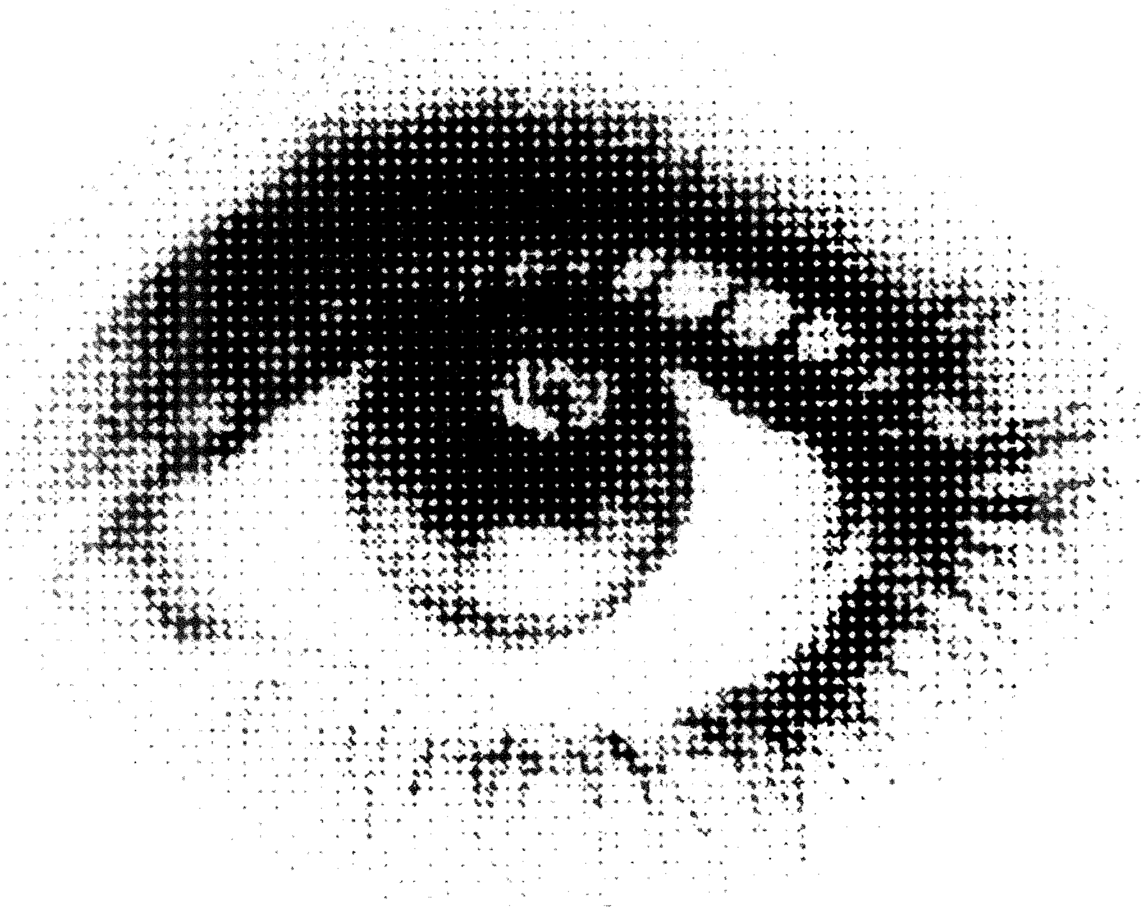
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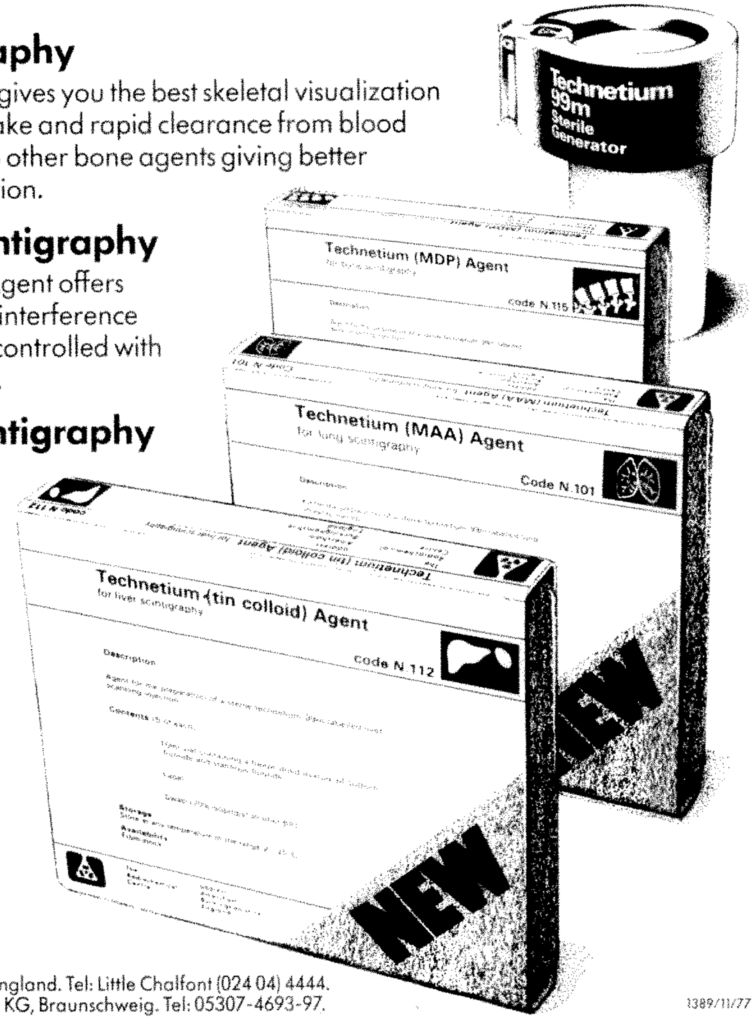

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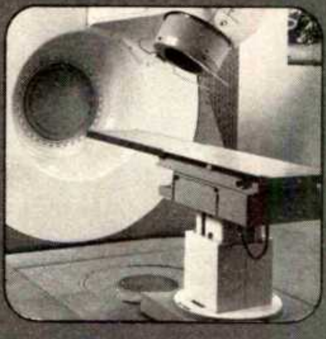

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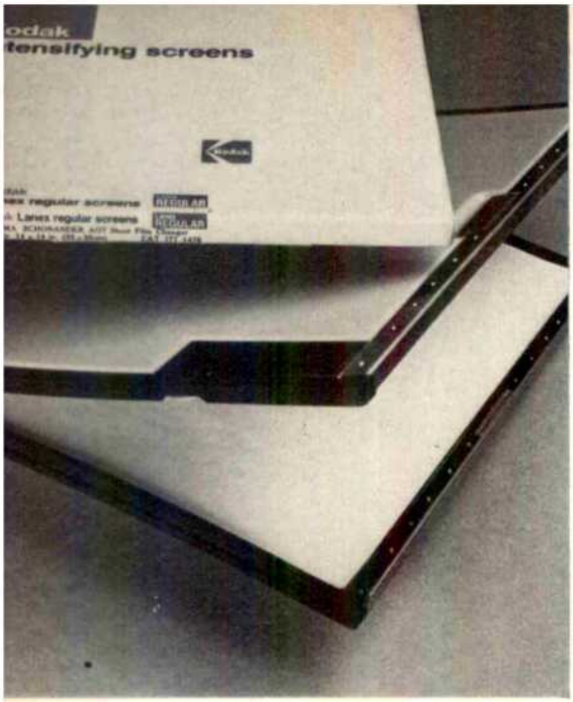

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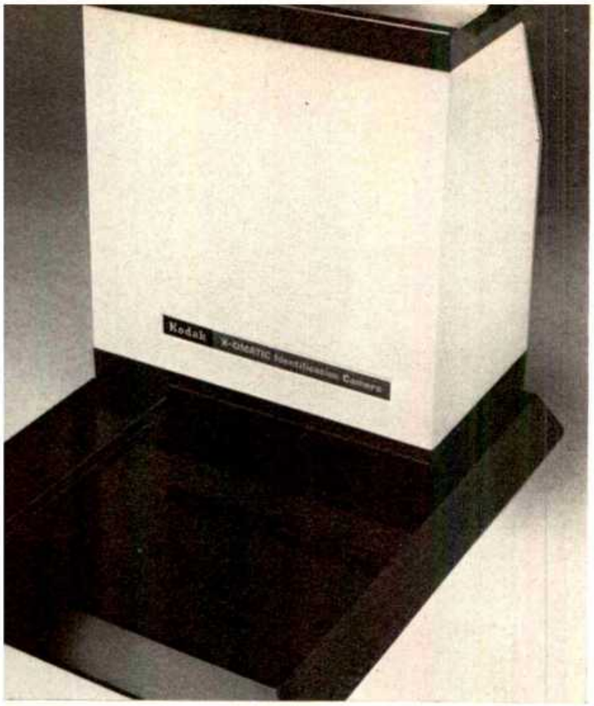

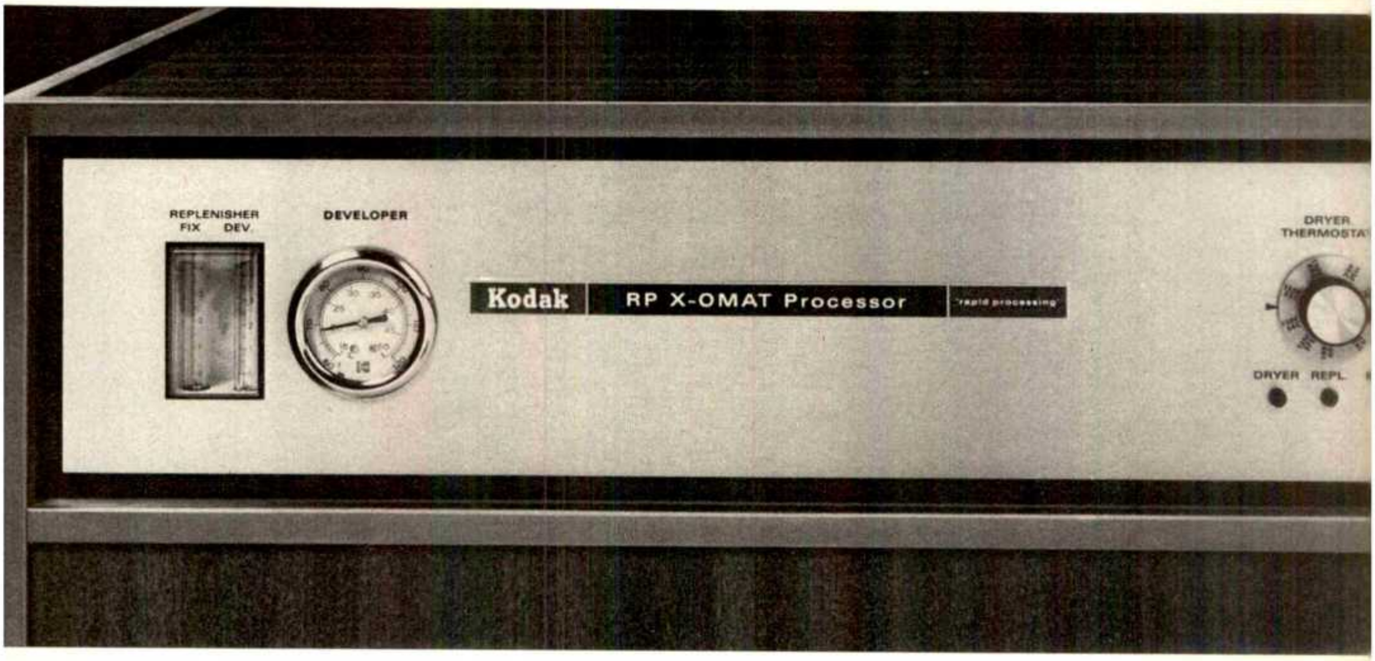

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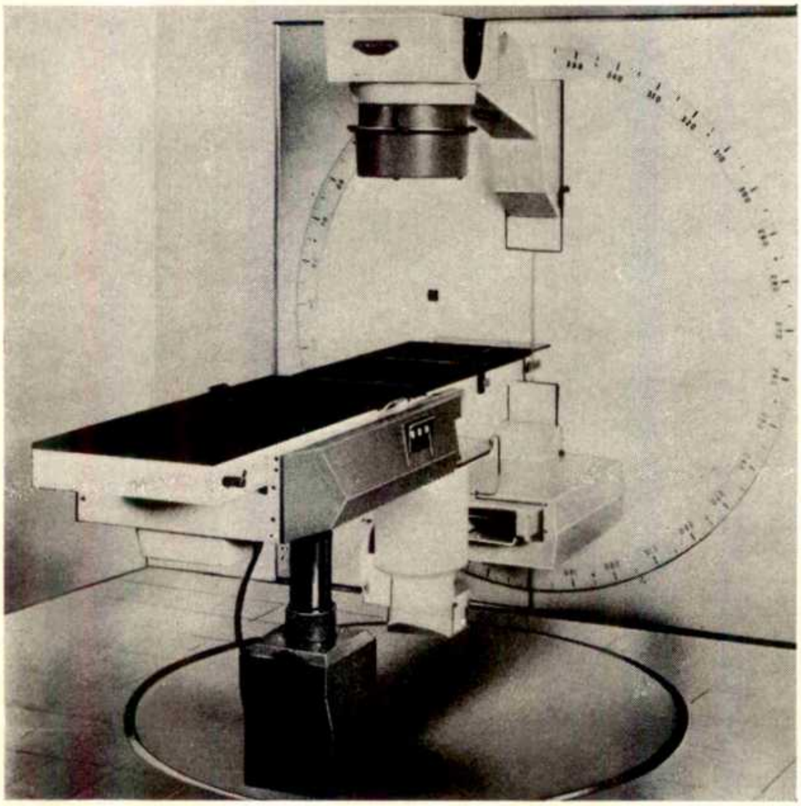

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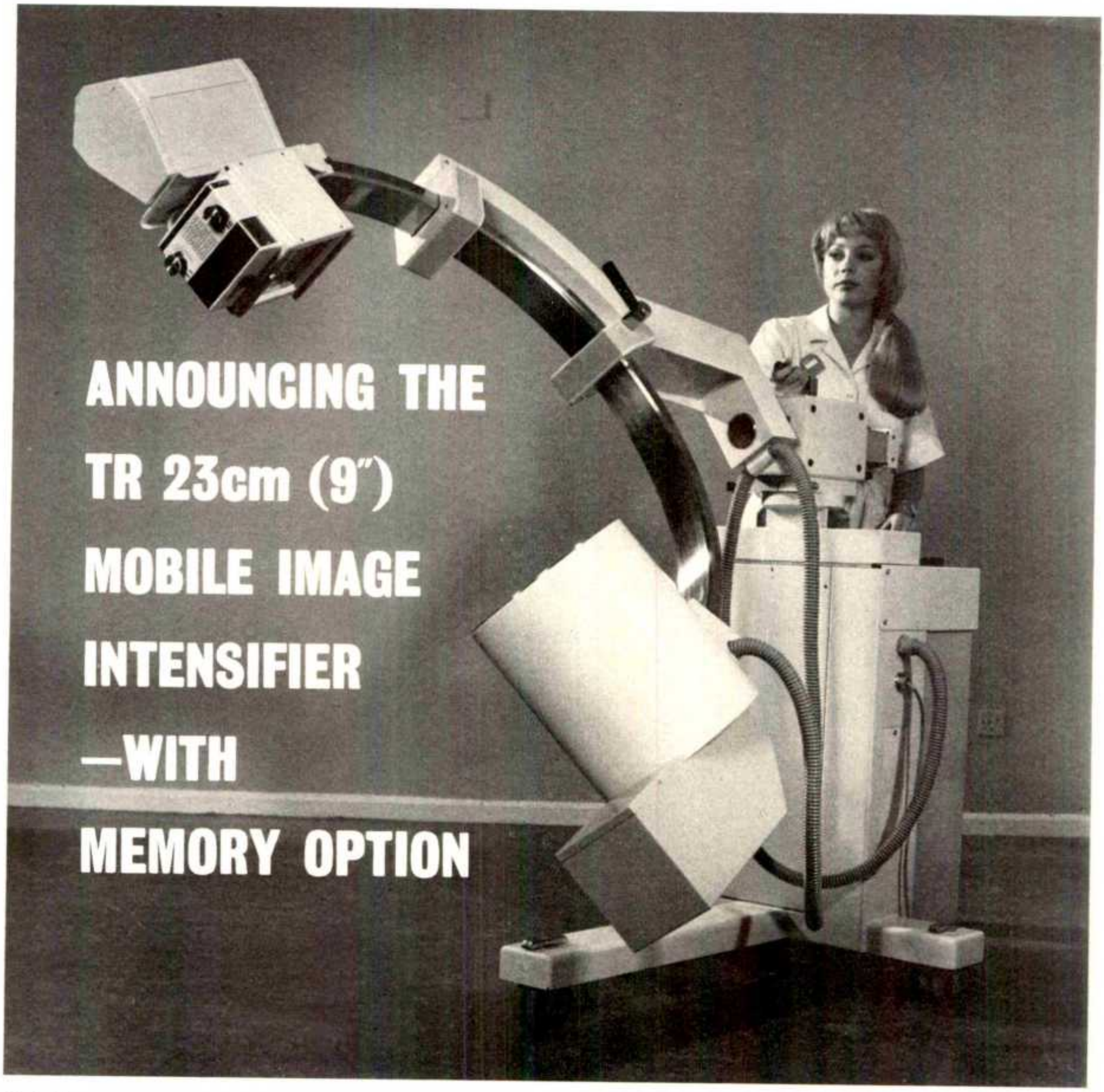

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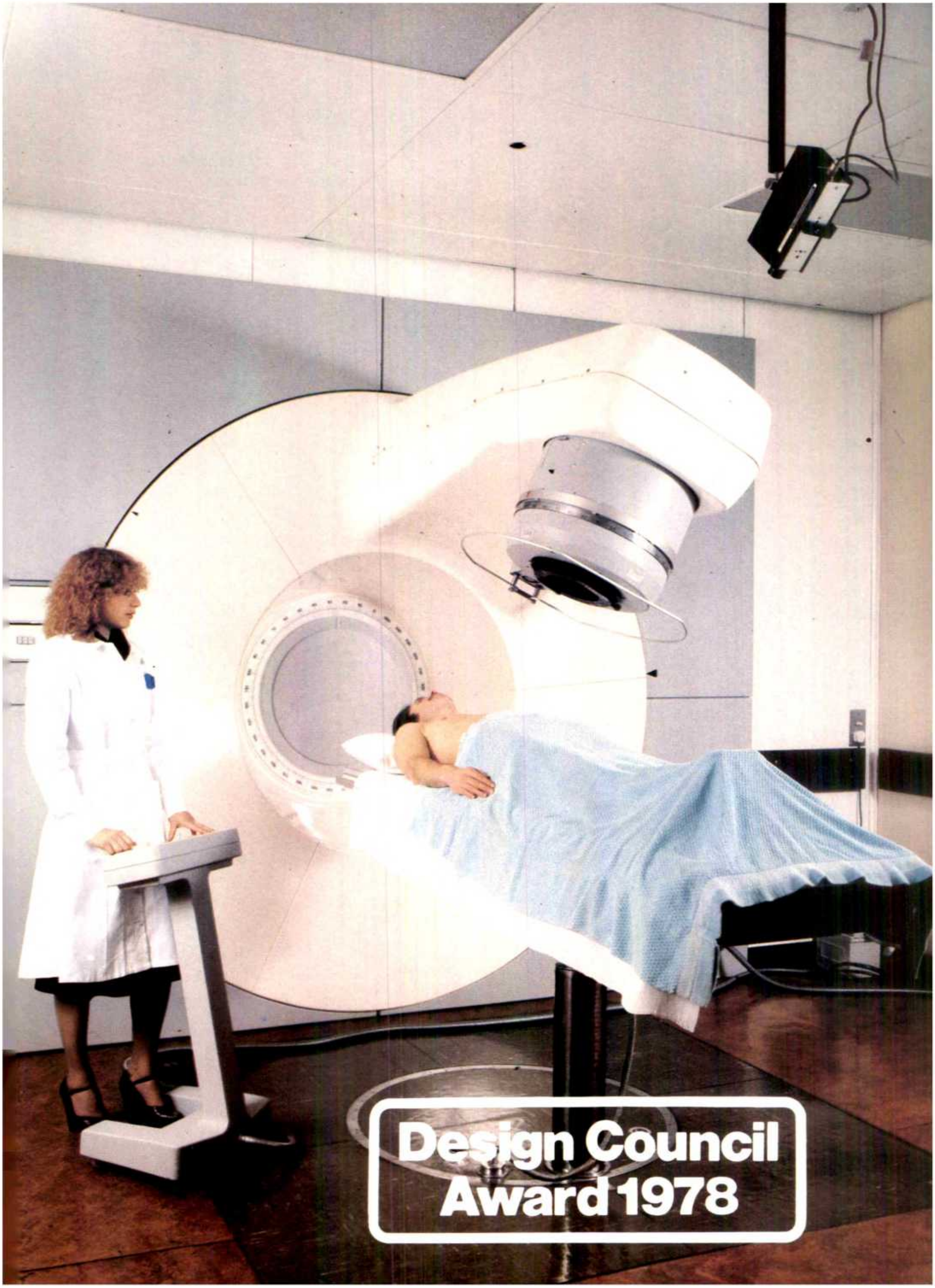
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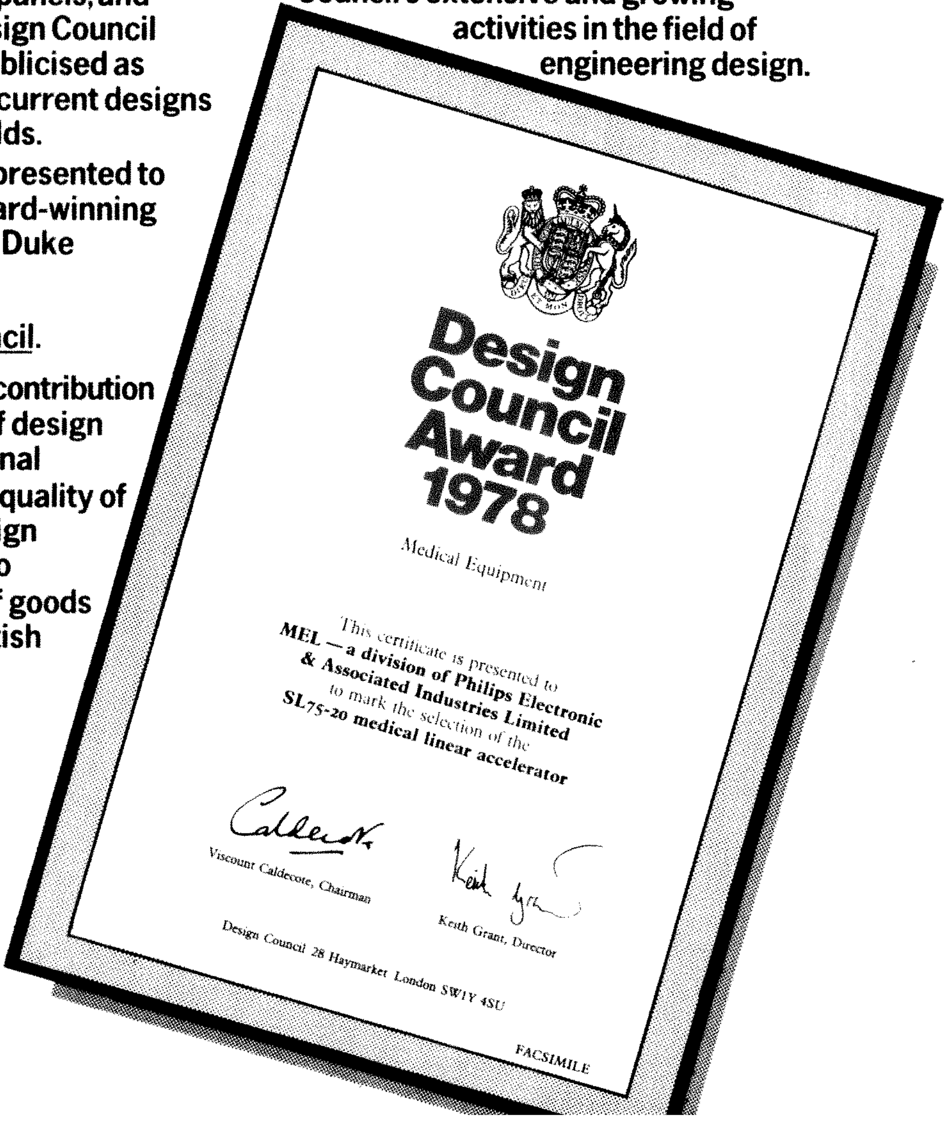

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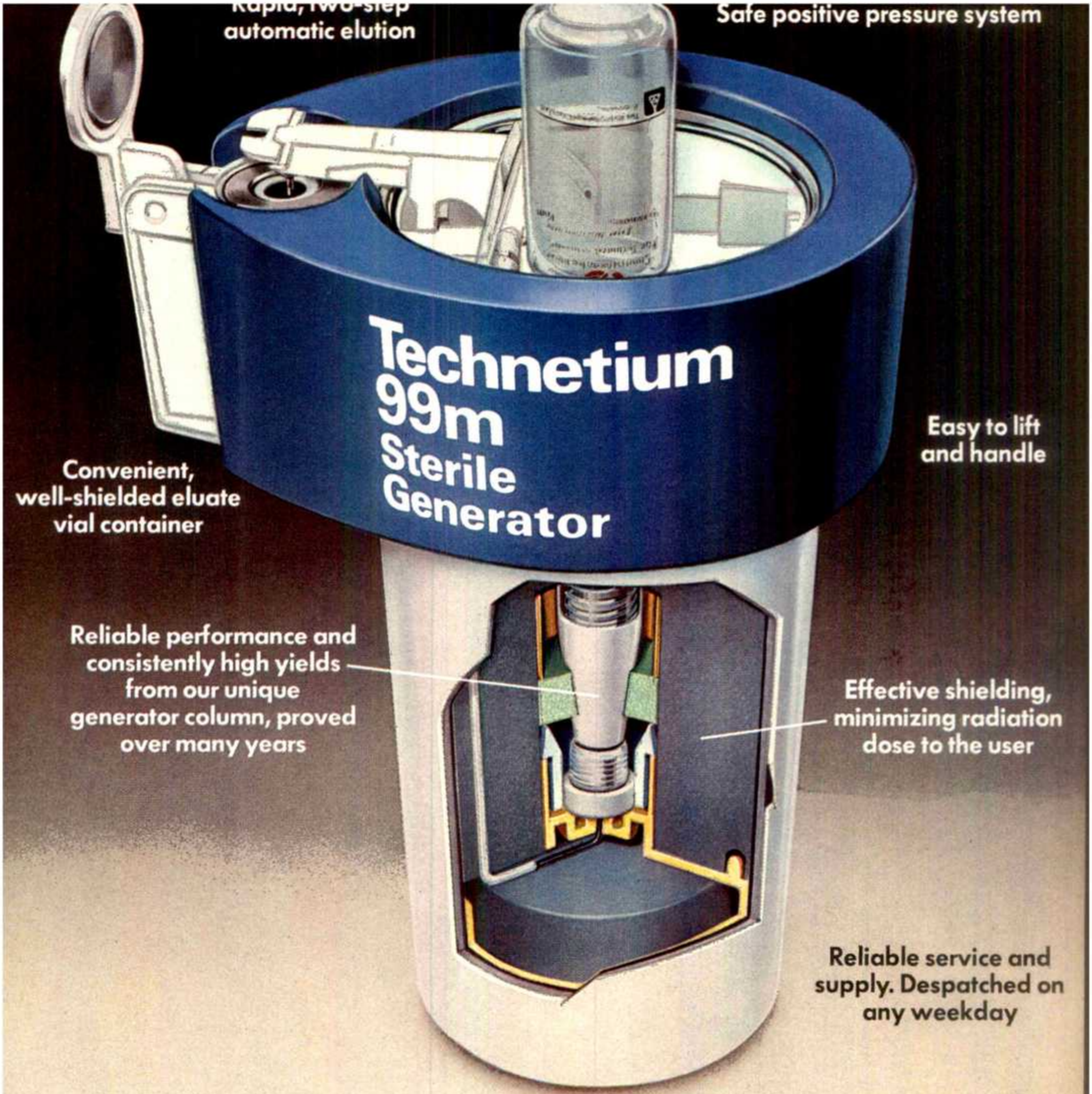
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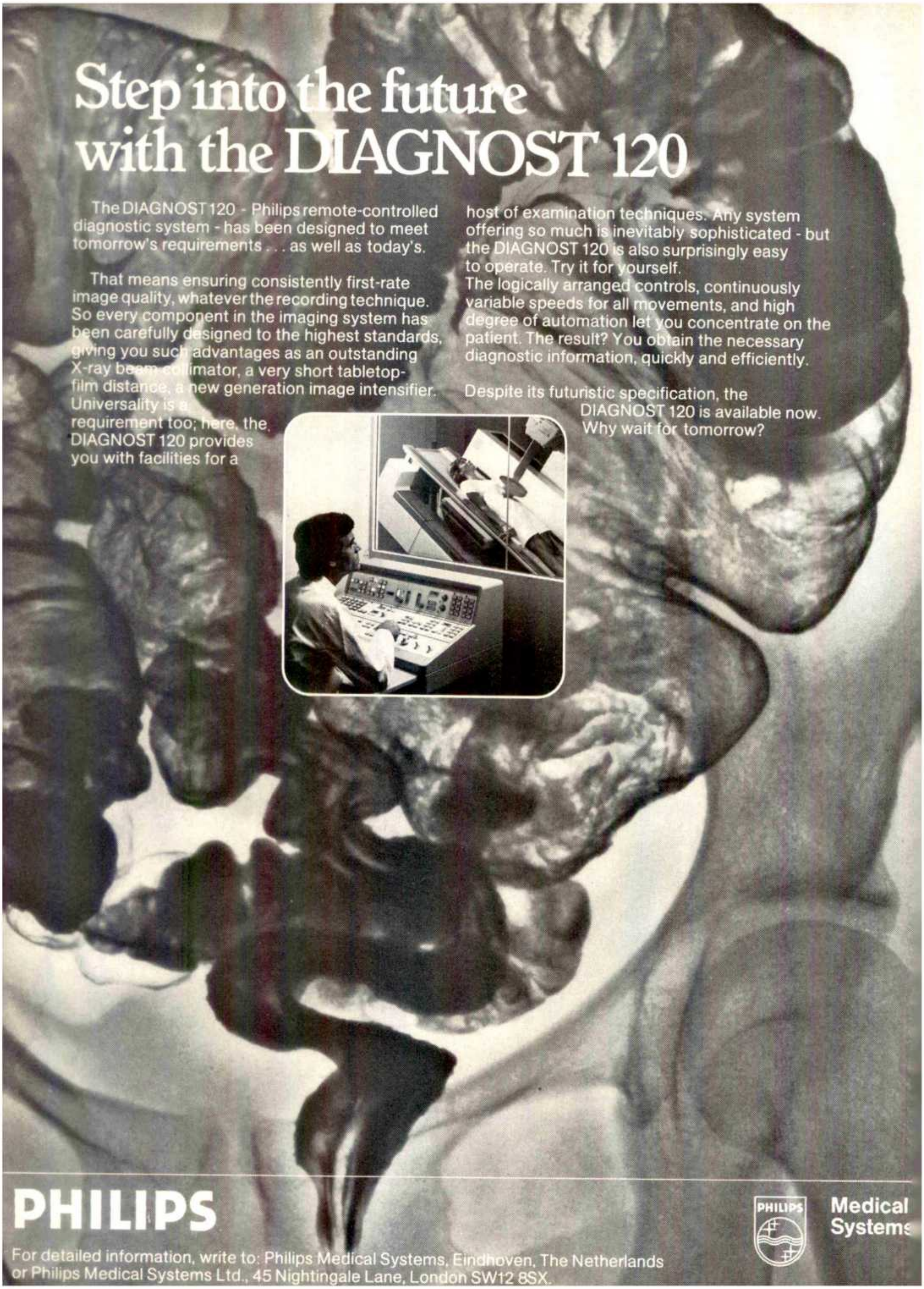

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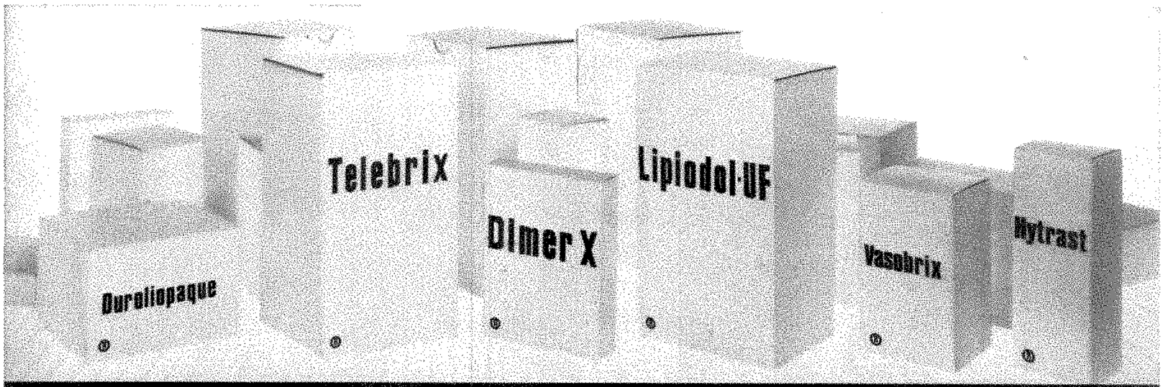

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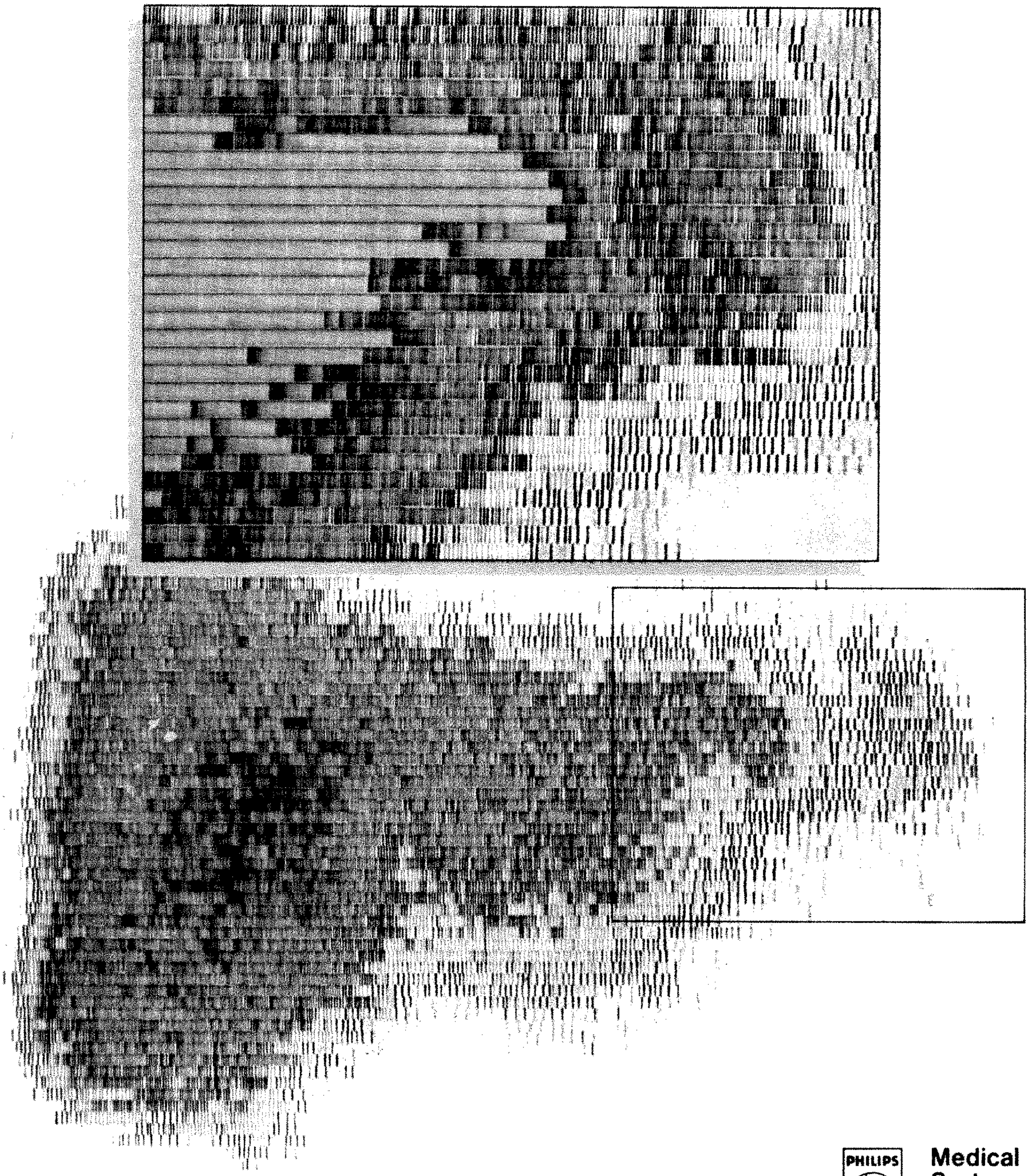

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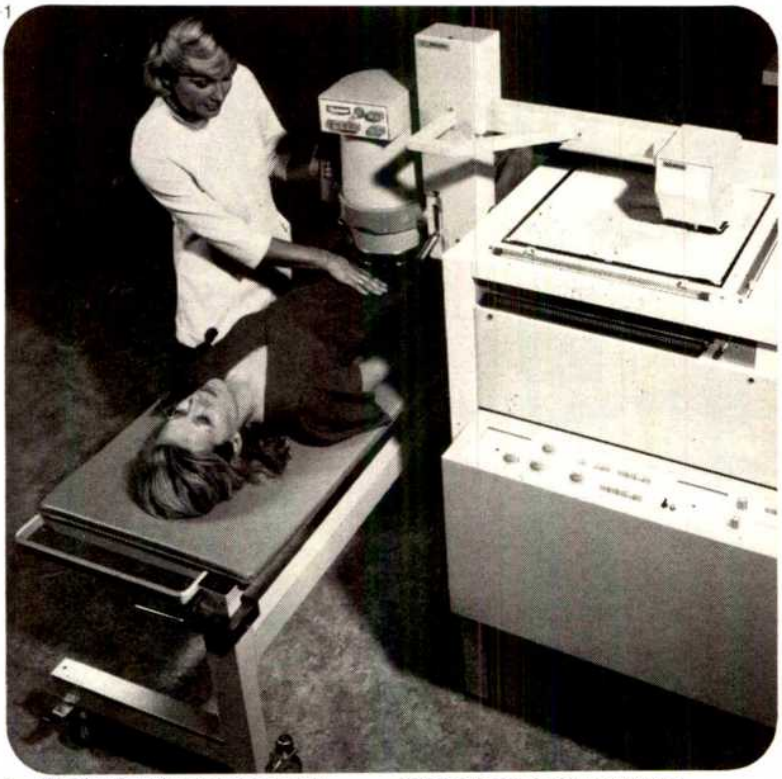
1



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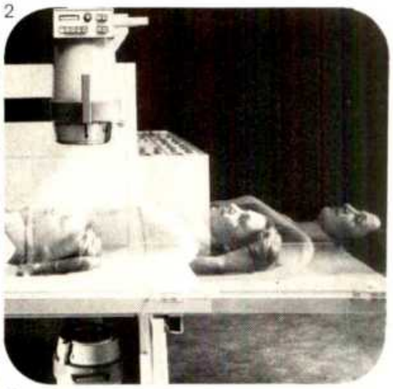

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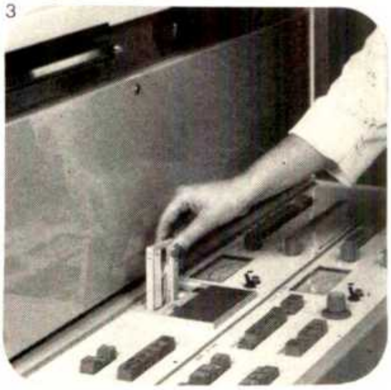

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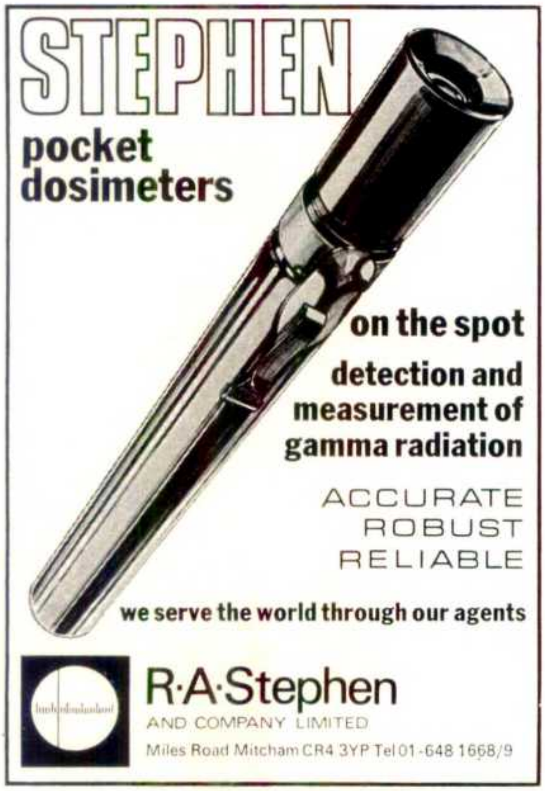

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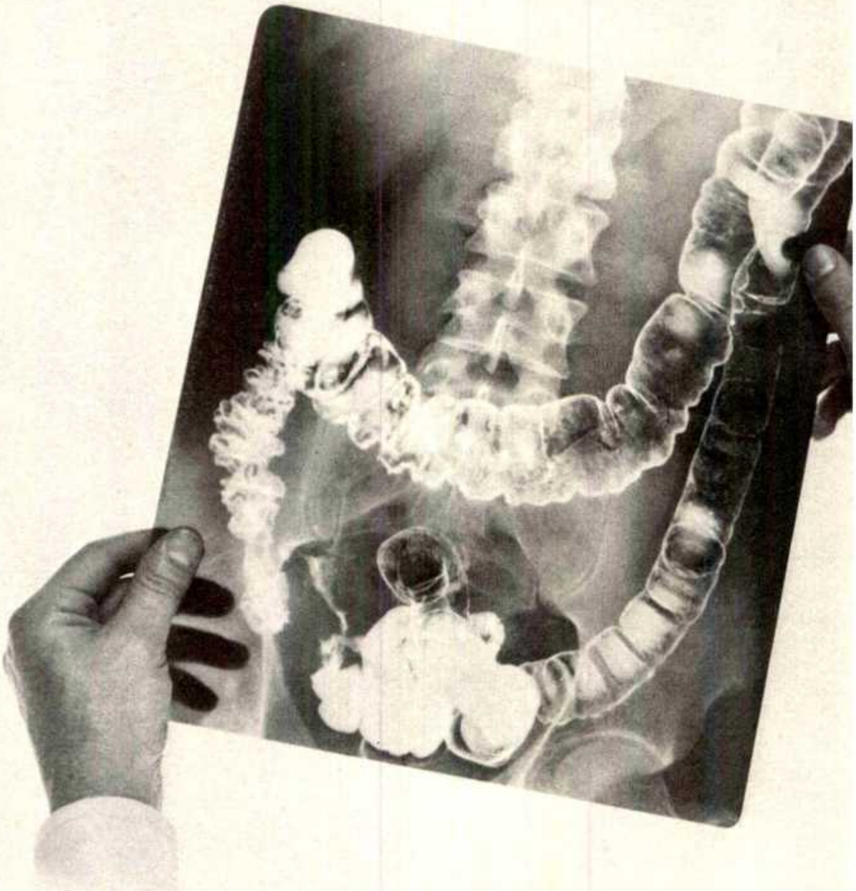

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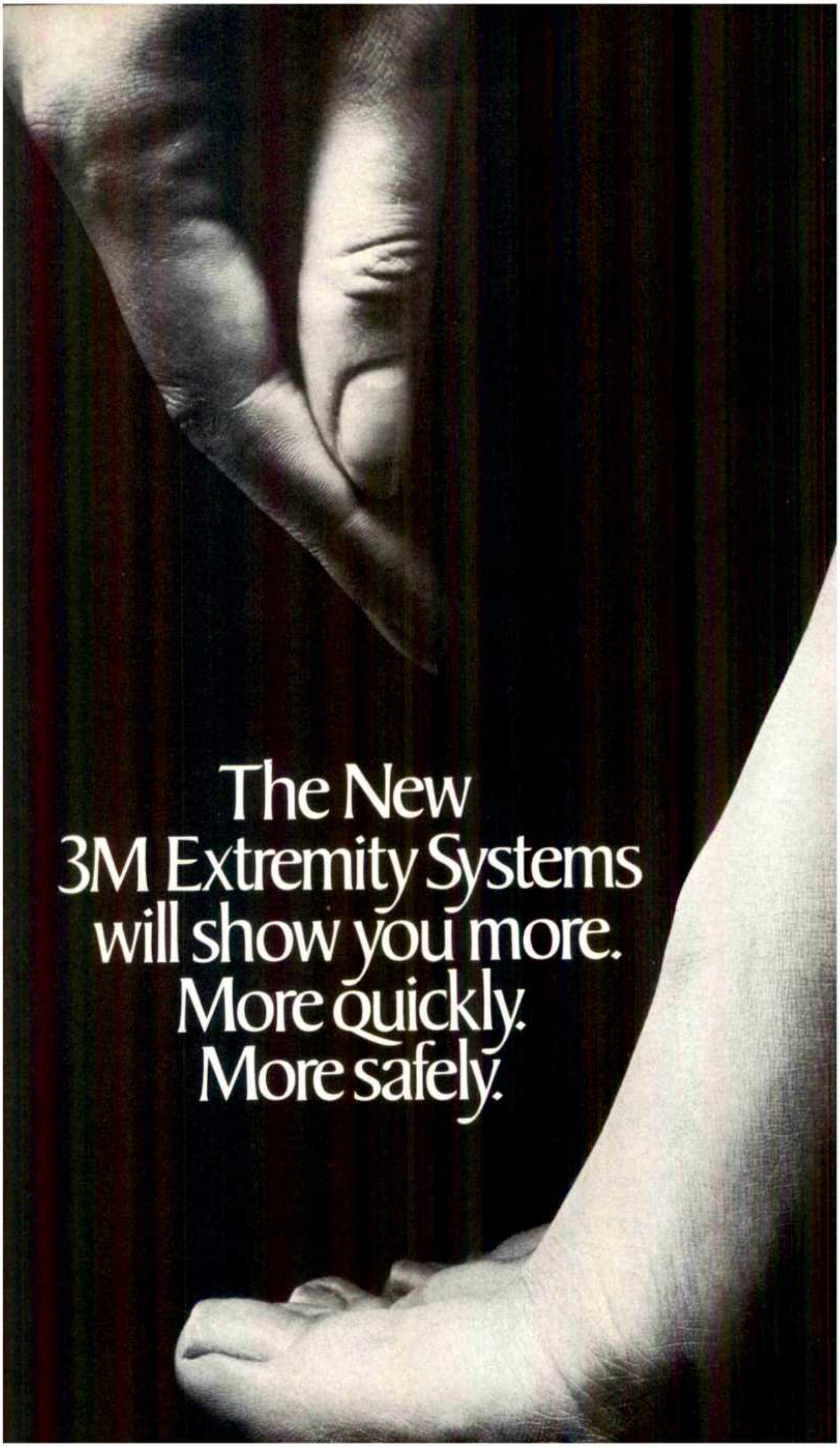
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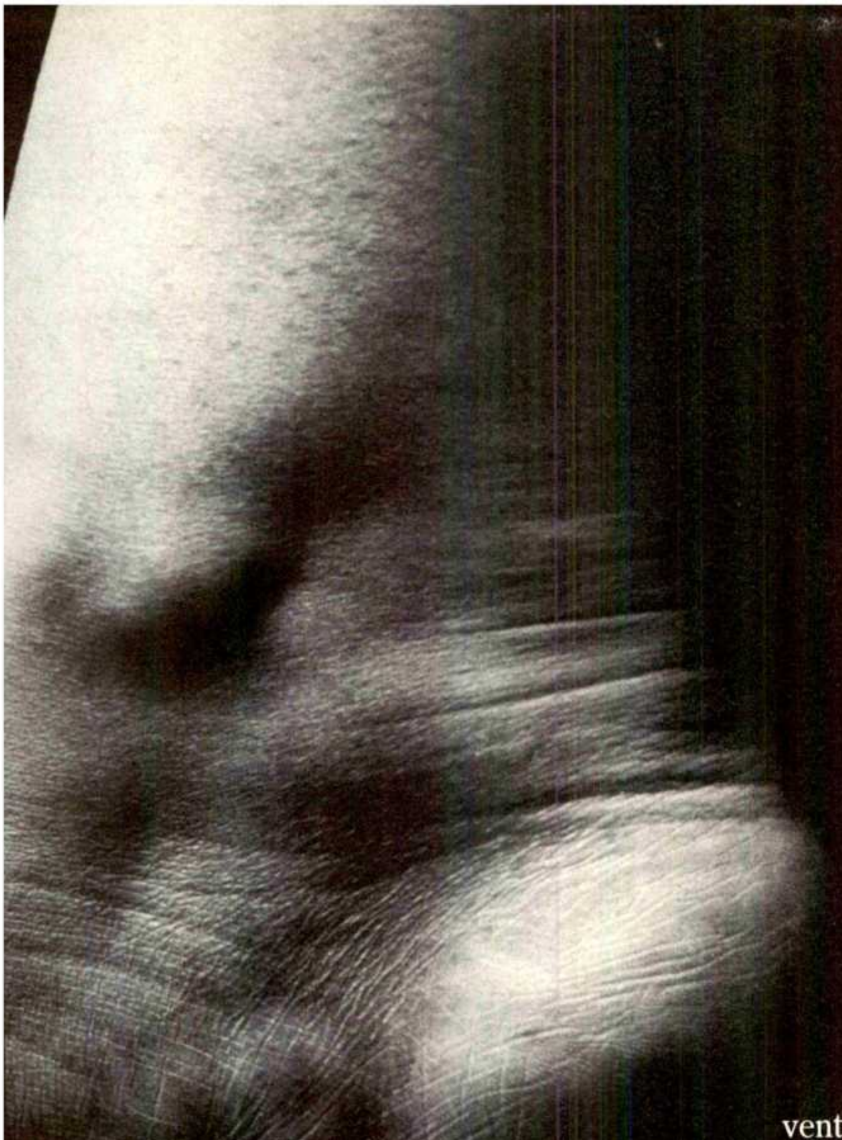

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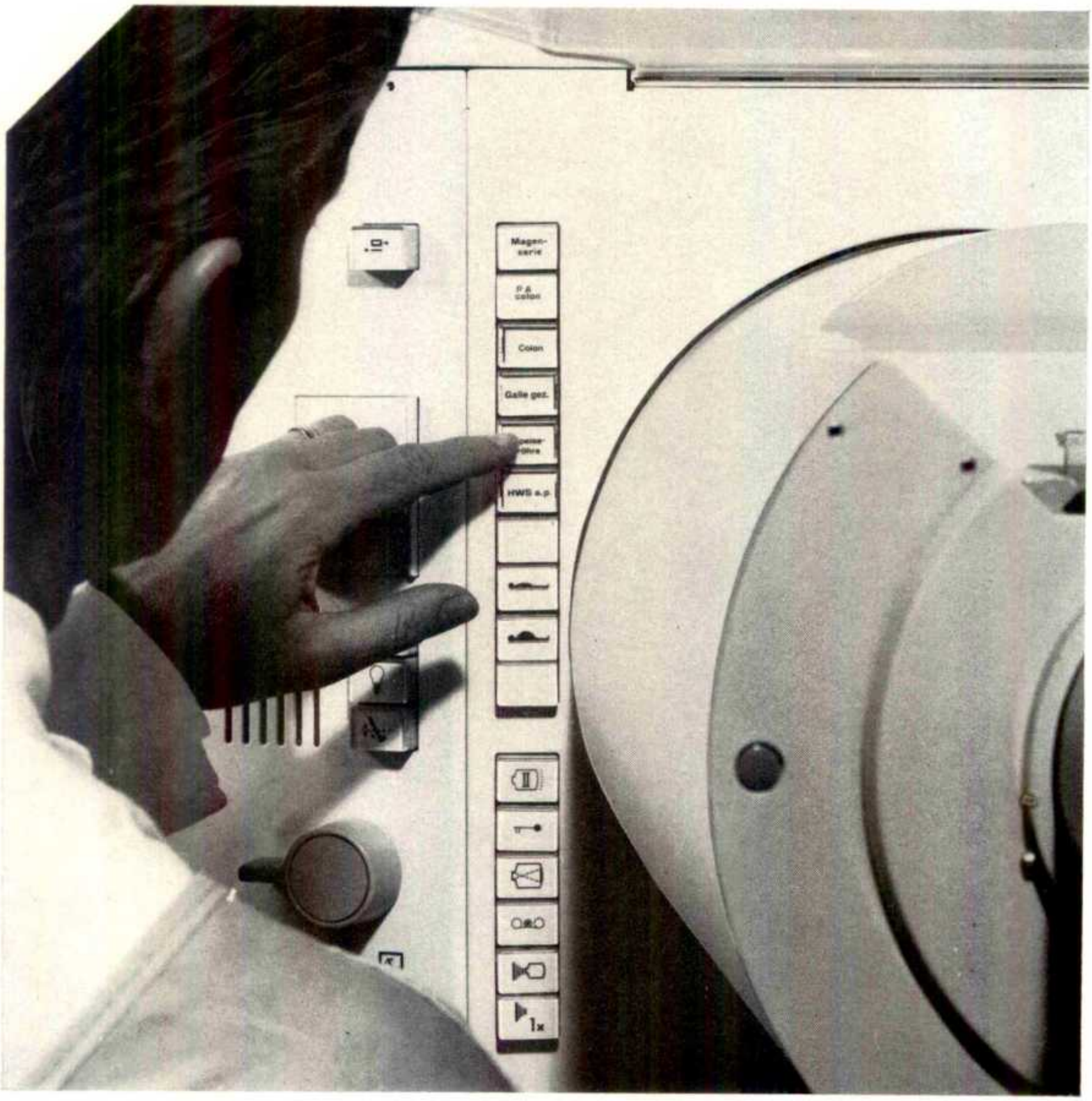

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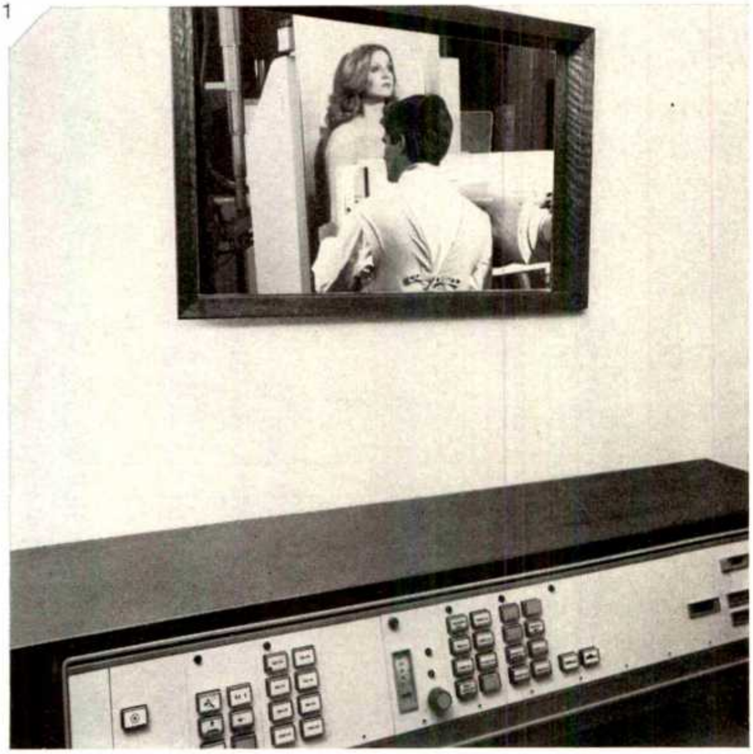

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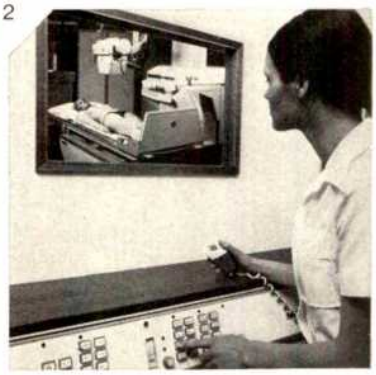

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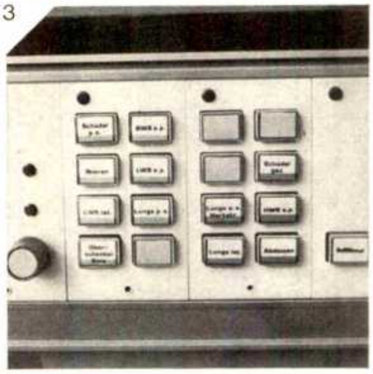

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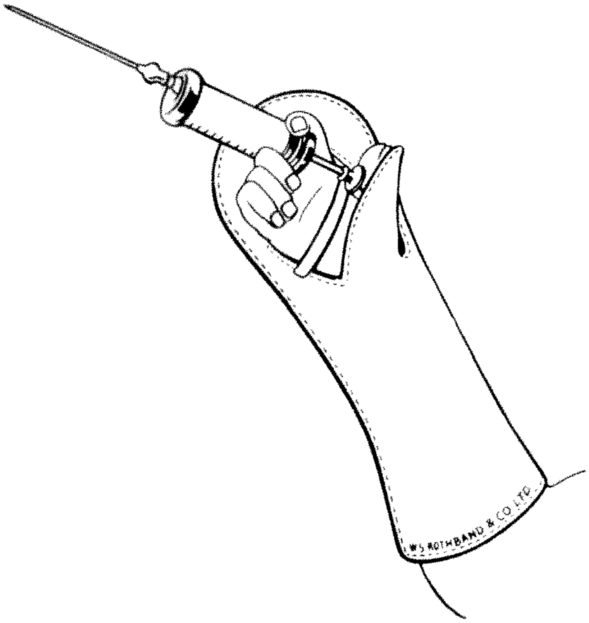
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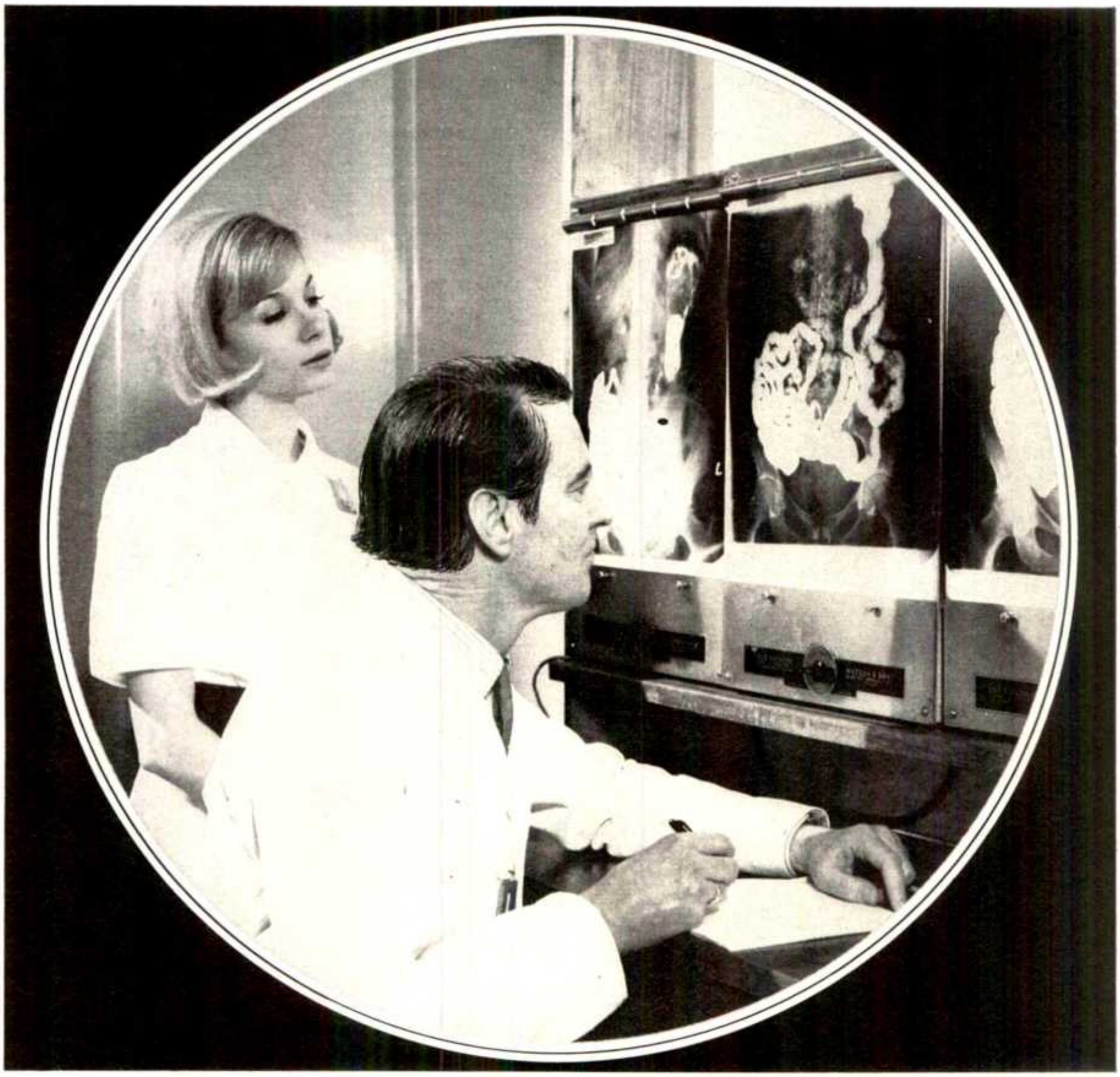

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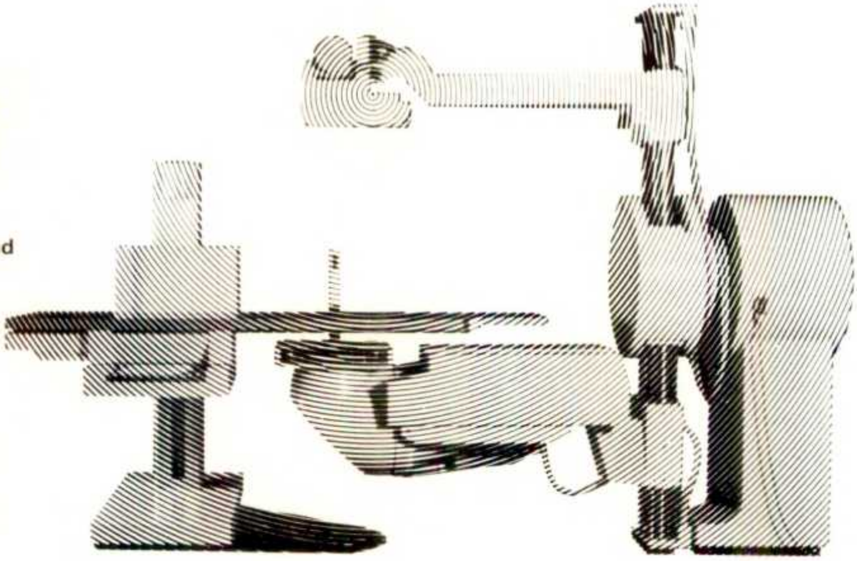

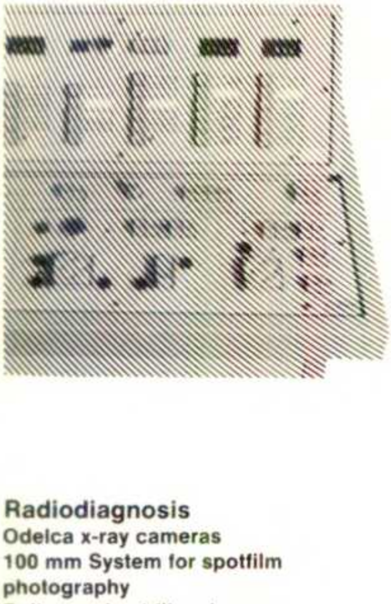

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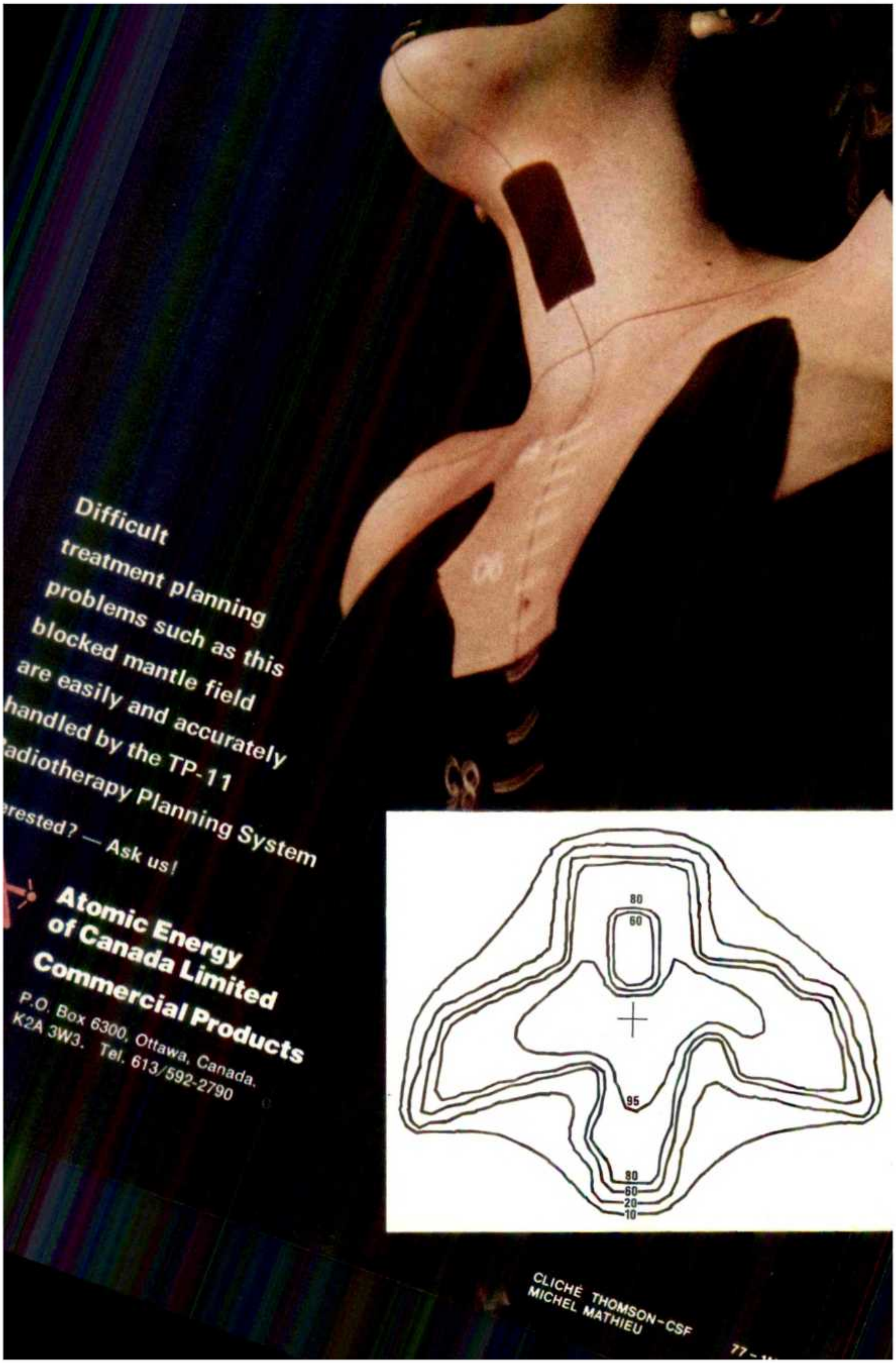
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VOLUME 51 NUMBER 605 MAY 1978

The British Journal of Radiology

Late meningeal effects of myelographic contrast media with special reference to metrizamide

By Elsemarie Berg Hansen, M.D., A. Fahrenkrug, M.D., and J. Praestholm, M.D.

Radiological Department I, Bispebjerg Hospital and Radiological Department, Hvidovre Hospital, Copenhagen, Denmark

(*Received November, 1977*)

ABSTRACT

Two hundred and fifty-six myelograms in 192 patients were followed by repeat myelography using a water-soluble contrast medium. The films of these re-examinations were analysed for signs of meningeal changes. Adhesive arachnoiditis had developed in five of 46 cases after methiodal sodium, in 24 of 96 cases after iothalamate meglumine, in seven of 12 cases after iocarmate meglumine, in seven of ten cases after iodophendylate, but in none of 90 cases after metrizamide. Dose of contrast medium, observation time and protein concentration of the CSF were found to be factors of importance for the development of adhesive arachnoiditis.

Water-soluble contrast media have been used extensively for lumbar myelography in Scandinavia and other European countries, since they allow very reliable diagnosis of disc herniation. The introduction of better contrast media has constantly lowered the incidence of acute side effects, which in lumbar myelography with metrizamide are approaching the level of side effects of simple lumbar puncture (Grainger *et al.*, 1976; Hansen *et al.*, 1976). Adhesive arachnoiditis is a serious late side effect, not only of the oily contrast media, but also the absorbable water-soluble media hitherto employed. Metrizamide has been in clinical use in our departments since November 1973. This investigation is an attempt to evaluate the incidence of adhesive arachnoiditis after myelography with metrizamide, as compared with other contrast media.

MATERIAL AND METHOD

From November 1973 to March 1977 a total of 1230 lumbar myelograms were performed using metrizamide. Ninety of these myelograms were re-examinations with metrizamide and constituted the material evaluated for myelographic changes after metrizamide. The patients examined during the first 22 months, on whom myelography with contrast media other than metrizamide had previously been performed, were selected as material for comparison; in these the following contrast media had been employed: methiodal sodium (Abrodil, Conturex, Kontrast-U) in 46 myelograms, iothalamate meglumine (Conray) in 96, iocarmate meglumine (Dimer-X) in 12, iodophendylate (Myodil, Pantopaque) in ten, and oxygen in two myelograms. The total material thus comprised 256 repeat myelograms which could be compared with the original myelograms. The number of patients was 192: 142 patients had undergone two myelograms, 37 patients three myelograms, 12 patients four myelograms, and one patient five myelograms. The distribution of age and sex at the time of the primary myelography is shown in Table I.

Technique of myelography

The doses of water-soluble contrast media employed for the primary myelograms are shown in Table II. The dose of iodophendylate was 9 ml, which was evacuated, although incompletely, after the examination. All myelograms with iothalamate meglumine and iocarmate meglumine with doses higher than 1420 mg I were performed in other hospitals. Lumbar injection of contrast medium in

TABLE I

AGE AND SEX DISTRIBUTION AT THE TIME OF PRIMARY MYELOGRAPHY

	15–29 years	30–44 years	45–60 years	> 60 years	Total
Male	10	51	42	3	106
Female	11	39	33	3	86

TABLE II

Incidence of post-myelographic arachnoiditis in relation to nature and dose of water-soluble contrast medium employed

Contrast medium	Dose of water-soluble contrast medium used at the previous myelography											
	≤1040 mg I			1041–1419 mg I			1420–1999 mg I			≥2000 mg I		
	Examinations	Arachnoiditis		Examinations	Arachnoiditis		Examinations	Arachnoiditis		Examinations	Arachnoiditis	
	N	n	%	N	n	%	N	n	%	N	n	%
Methiodal Sodium	44	4	9	1	0		1	1	100			
Iothalamate meglumine	0			78	14	18	8	4	50	10	6	60
Iocarmate meglumine	1	0		5	1	20	4	4	100	2	2	100
Metrizamide	0			90	0	0						

TABLE III

The influence of a subsequent operation on the incidence of post-myelographic arachnoiditis

Contrast medium	Patients operated upon between the examinations			Patients not operated upon between the examinations		
	Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis	
	N	n	%	N	n	%
Methiodal sodium	35	4	11	11	1	9
Iothalamate meglumine	74	19	26	22	5	23
Iocarmate meglumine	7	6	86	5	1	20
Metrizamide	73	0	0	17	0	0
Iodophendylate	7	4	57	3	3	100
Oxygen	0	0		2	0	0

our departments is performed with the patient in the upright sitting position. After the injection the patient is placed in the supine position with the head end of the table elevated 20 deg. Our technique of myelography with metrizamide has previously been described in detail (Hansen *et al.*, 1976). In 19 of the primary myelograms 8 ml metrizamide 170 mg I/ml, isotonic with the CSF, was employed, and in 71 myelograms 5 ml metrizamide 280 mg I/ml.

Signs of adhesive arachnoiditis

Adhesive arachnoiditis was diagnosed if one or more of the following radiological signs were demonstrated on the water-soluble contrast medium myelogram:

(1) Non-filling of the sacral and lower lumbar root-pockets, usually symmetrically distributed.
(2) Incomplete filling of root-pockets compared with the original myelogram.
(3) Disappearance of the normal cauda equina-striation of the lower part of the contrast column.
(4) Narrowing of the caudal sac.

Irregular indentations and incomplete filling of a single root-pocket at the site of a previous operation were interpreted as defects due to scar tissue formation from the operation and not as indicative of arachnoiditis.

Results

Radiological signs of adhesive arachnoiditis were found in 43 myelograms: in five of 46 cases (11%) after methiodal sodium, in 24 of 96 cases (25%) after iothalamate meglumine, in seven of 12 cases (58%) after iocarmate meglumine, in seven of ten cases (70%) after iodophendylate, but in no case after 90 myelograms with metrizamide.

The occurrence of adhesive arachnoiditis was shown to be dependent on the dose of the water-soluble contrast medium (Table II). The higher the dose, the greater the incidence of adhesive arachnoiditis.

The material has been further analysed to discover whether the treatment of the patients or conditions in the patient might have been the cause of the arachnoiditis.

TABLE IV

The influence of the interval between myelography and operation on the incidence of post-myelographic arachnoiditis

Contrast medium	Interval between myelography and operation											
	≤6 days			7–30 days			>30 days			No operation		
	Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis	
	N	n	%	N	n	%	N	n	%	N	n	%
Methiodal sodium	16	0		15	2	13	4	2	50	11	1	9
Iothalamate meglumine	43	9	21	24	8	33	7	2	29	22	5	23
Iocarmate meglumine	7	6	86	0			0			5	1	20
Metrizamide	50	0	0	19	0	0	4	0	0	17	0	0
Iodophendylate	4	3	75	3	2	67	0			3	3	100
Oxygen										2		0

TABLE V

The influence of time on the incidence of post-myelographic arachnoiditis

Contrast medium	Interval between two myelographies							
	<1 month		1 month – 1 year			>1 year		
	Re-examinations	Arachnoiditis	Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis	
	N	n	N	n	%	N	n	%
Methiodal sodium	2	0	3	0		41	5	12
Iothalamate meglumine	4	0	11	2	18	81	22	27
Iocarmate meglumine	1	0	2	1	50	9	6	67
Metrizamide	5	0	61	0		24	0	
Iodophendylate	0		2	0		8	8	100
Oxygen			1	0		1	0	

TABLE VI

The influence of the CSF protein concentration on the incidence of post-myelographic arachnoiditis

Contrast medium	Protein concentration of the CSF at the previous myelography									
	<50 mg %			50–70 mg %			>70 mg %			Unknown
	Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis		Re-examinations	Arachnoiditis		Re-examinations
	N	n	%	N	n	%	N	n	%	N
Methiodal sodium	26	3	12	7	0		6	1	17	7
Iothalamate meglumine	64	12	19	17	6	35	7	3	43	8
Iocarmate meglumine	10	5	50	1	1	100	1	1	100	0
Metrizamide	63	0		16	0		5	0		6
Iodophendylate	6	5	83	1	0		1	1	100	2
Oxygen	2	0								

The material was divided into patients operated upon and not operated upon after myelography. As can be seen in Table III, a subsequent operation tended to increase the frequency of adhesive arachnoiditis.

The interval between myelography and the subsequent operation has been claimed to be of importance for the development of arachnoiditis. This has not been verified in our material (Table IV).

The observation period, *i.e.* the interval between the original and subsequent myelogram, proved to be of importance (Table V), as the frequency of adhesive arachnoiditis rose with increasing interval between the two myelograms.

The age and sex of the patients did not influence the frequency of adhesive arachnoiditis.

The protein concentration of the CSF at the primary myelography was of some importance, as higher frequencies of adhesive arachnoiditis were seen with increasing protein concentration (Table VI).

Discussion

Neurosurgeons are very conservative with regard to intradural explorations in patients with adhesive arachnoiditis, and therefore relatively few of the cases demonstrated by myelography have been verified by operation and histological examination.

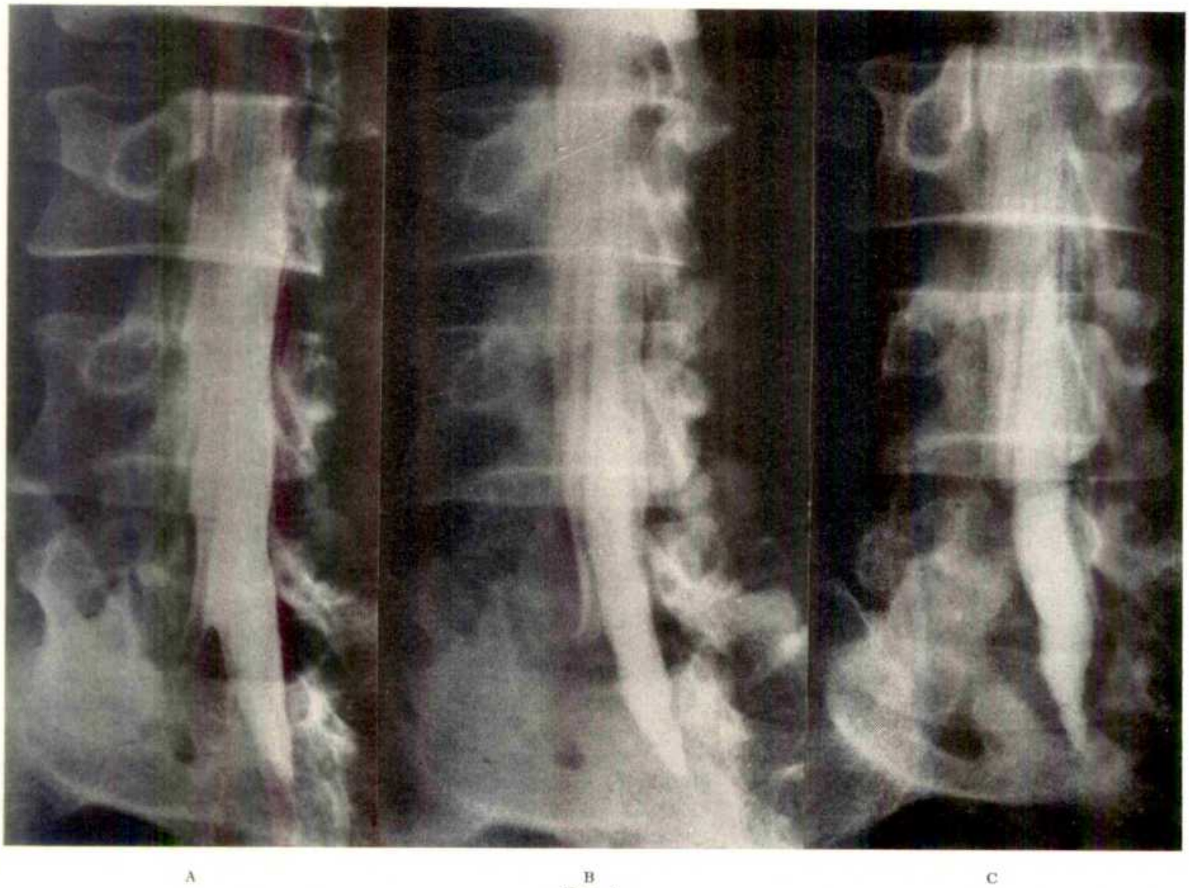

Fig. 1.

(A) Lumbar myelogram (right oblique position) using 7.5 ml iothalamate meglumine 282 mg I/ml in a 37-year-old male complaining of recurrent lumbar pain with radiation to the right leg. Normal root-pockets and contour of the spinal canal were found. No improvement was seen during physiotherapy.

(B) A second myelogram six months later using 5 ml iothalamate meglumine 282 mg I/ml revealed signs of adhesive arachnoiditis with obliteration of sacral root-pockets, narrowing of the caudal sac, and disappearence of the cauda equina striation. A subsequent operation revealed the right 1. sacral root to be fixed by an old, free prolapse, which was removed without opening the dura.

(C) Five years later a third myelogram was performed with 8 ml metrizamide 170 mg I/ml because of recurrence of symptoms. The adhesive arachnoidtis showed slight progression. At operation the sacral dural sac was opened. No fila radicularia were found in the subarachnoid space as they were tightly bound to the dura within thickened arachnoid matter. A biopsy of the arachnoid showed fibrous tissue with parallel bundles of collagen fibrils with only few fibrocytes.

The radiological picture of adhesive arachnoiditis, is, however, quite characteristic, and there are no obvious diagnostic pitfalls. It has been described following both oily (Moseley, 1977; Teng and Papatheodorou, 1967; Smith and Loeser, 1972) and water-soluble contrast media (Cronqvist and Fuchs, 1964; Halaburt and Lester, 1973). In adhesive arachnoiditis the root-pockets agglutinate, and the nerve roots of the cauda equina glue together, forming a thick bundle in the subarachnoid lumen (Cronqvist and Fuchs, 1964), or else the nerve roots adhere to the arachnoid and dura, resulting in a characteristic narrowing of the caudal sac and loss of the cauda equina striation (Smith and Loeser, 1972).

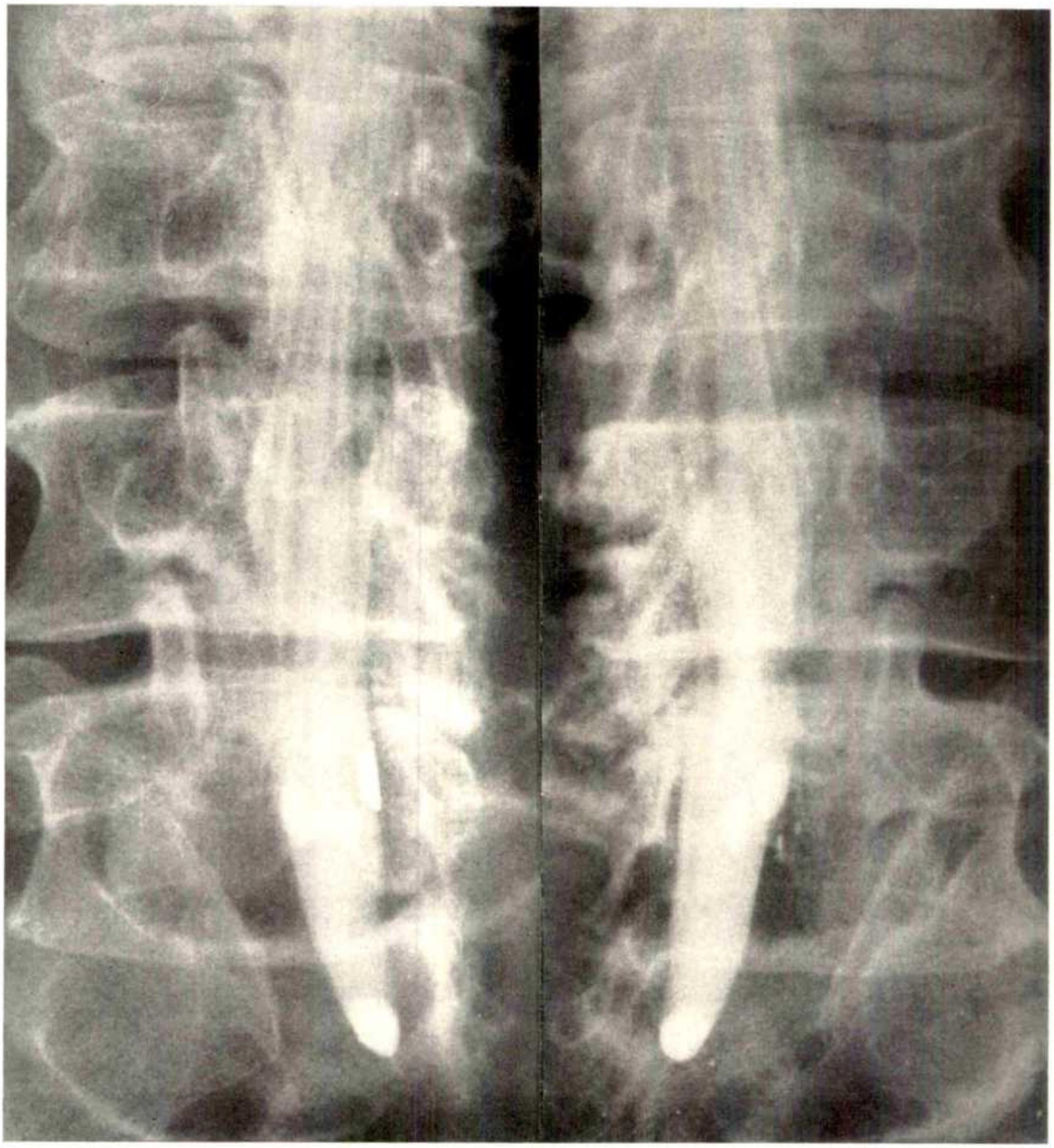

FIG. 2.

Lumbar myelography (both oblique positions) using 5 ml metrizamide 280 mg I/ml in a 61-year-old female with lumbago. Signs of adhesive arachnoiditis with obliteration of root pockets and loss of cauda equina striation are shown. Thirty-one months earlier an iodophendylate myelogram had been performed because of neck pain. No prolapse was found. 9 ml of Pantopaque were injected, 4 ml of which were evacuated after this examination.

One single case in the present series in which intradural operation was performed verified this (Fig. 1).

A number of case reports of adhesive arachnoiditis after myelography with oily contrast media have been published (Hurteau *et al.*, 1954; Bucy and Speigel, 1943; Tarlov, 1945; Sarkisian, 1956), and recently a more extensive study has been reported, where in our opinion oil myelography may have played a part in the aetiology of adhesive arachnoiditis (Moseley, 1977).

Lumbar iothalamate meglumine myelography became increasingly popular in the late sixties (Ahlgren, 1969; Gonsette and André-Balisaux, 1968; Praestholm and Lester, 1970), and the first report of adhesive arachnoiditis after this examination was rapidly published (Autio *et al.*, 1972). The diagnosis of adhesive arachnoiditis by means of water-soluble contrast medium myelography (Cronqvist and Fuchs, 1964) had its renaissance, and several articles reporting adhesive arachnoiditis after myelography with water-soluble contrast media have since been published (Ahlgren, 1973; Halaburt and Lester, 1973; Irstam and Rosencrantz, 1973; 1974; Liliequist and Lundström, 1974; Skalpe, 1976). It was now recognized that the hitherto employed water-soluble sodium methiodal could also be responsible for this effect, a possibility first mentioned in 1972 by Bidstrup.

We did not find adhesive arachnoiditis after myelography with metrizamide. This agrees with the findings of Skalpe, 1976, who reported 77 repeat myelograms with metrizamide employing doses of 1700 to 3000 mg I. In only one patient with adhesive arachnoiditis due to previous methiodal myelography, succeeded by operation, did he find a minor progression of the changes after metrizamide.

Among other aetiological factors investigated, we found the dose of contrast medium to be the most closely correlated to the development of adhesive arachnoiditis (Table II). This correlation was first described for iothalamate meglumine by Halaburt and Lester, 1973, and for iocarmate meglumine by Ahlgren, 1973. For iothalamate meglumine Ahlgren was not able to find any correlation between dose of contrast medium and frequency of adhesive arachnoiditis. However, Irstam *et al.*, 1974, assumed that the differences in incidence of adhesive arachnoiditis after iothalamate meglumine in their material and Ahlgren's could be explained by difference in dose, an opinion which is supported by our results. Our low incidence of adhesive arachnoiditis after methiodal sodium may also be explained by the low dose employed, compared with higher doses of contrast medium and higher frequencies of adhesive arachnoiditis reported by Ahlgren, 1973, and Liliequist and Lundström, 1974. The higher frequencies reported by Irstam *et al.*, 1974, may be explained by difference in technique. They performed the injection with the patient lying in the lateral position resulting in a high concentration of contrast medium on the same side of the spinal canal, while in Denmark we traditionally inject the contrast medium with the patient in the upright sitting position, thus producing greater dilution of the contrast medium with CSF.

Operation subsequent to myelography has previously been shown to increase the incidence of adhesive arachnoiditis significantly (Ahlgren, 1973; Irstam *et al.*, 1974; Liliequist and Lundström, 1974; Skalpe, 1976). This effect of surgery was not prominent in our material (Table III), which may be explained by the fact that a relatively large number of myelograms with high doses of iothalamate meglumine were among the unoperated patients, and contributed to the higher incidence of adhesive arachnoiditis in this group.

Our finding of an increasing incidence of adhesive arachnoiditis with increasing observation time (Table V) may be of special interest, even if Irstam *et al.*, 1974, and Skalpe, 1976, did not find any positive correlation of this nature in their materials. The method of selection of our material resulted in a shorter observation time for myelograms with metrizamide. Future studies with a longer observation period with metrizamide are therefore necessary.

A weak positive correlation between increased protein concentration in the CSF at primary myelography and the incidence of late adhesive arachnoiditis was found (Table VI). This correlation was first described by Halaburt and Lester, 1973, but not confirmed by Ahlgren, 1973. Animal experiments with injection of a mixture of iothalamate meglumine and homologous serum in the spinal canal of rabbits did not show any potentiation of the adverse effect of iothalamate meglumine on the leptomeninges by a high protein concentration in the CSF (Halaburt and Praestholm, unpublished data).

A very high incidence of adhesive arachnoiditis was found after the oily medium iodophendylate.

CONCLUSION

Adhesive arachnoiditis due to myelography or to myelography succeeded by operation is common with the water-soluble and oily contrast media hitherto employed. No leptomeningeal changes were discovered in our material of 90 re-examinations after lumbar myelography with metrizamide. Because of this superiority to other media, its low acute toxic effects, and the high diagnostic accuracy of water-soluble contrast medium myelography (Hansen *et al.*, 1976), we recommend that metrizamide be considered the medium of choice in lumbar myelography.

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Book review

Radiopharmaceutical dosimetry symposium. Edited and compiled by R. J. Cloutier, J. L. Coffey, W. S. Snyder & E. E. Watson, pp. ix+518, 1976 (U.S. Department of Health, Education and Welfare, Maryland) $6.20.

This is a report of the proceedings of a conference held at Oak Ridge in April 1976, sponsored by various organizations including the US Food and Drug Administration's Bureau of Radiological Health. Since the previous symposium, organized by Oak Ridge Associated Universities in 1969, there have been substantial changes in the range of radiopharmaceuticals used, and progress has been made in obtaining information concerning their retention by the body and in methods of dose calculation.

The symposium, with the stated objective to present the most up-to-date concepts of internal dosimetry techniques, was conducted in seven half-day sessions, followed by an imperfectly recorded panel discussion. Most of the 139 registered participants were based in centres in the USA, but speakers were selected to provide an overall coverage of the subject in some 40 separate contributions.

The papers were not entirely concerned with technique and useful indications are provided of the modifications to the dose delivered in abnormal and paediatric situations. W. S. Snyder and co-workers provide important data derived from considerations of the dose potentially delivered to the stomach wall, bladder, gonads and fetus. The dosimetry of particular radiopharmaceuticals such as 6-^{131}I-iodomethyl-19-norcholesterol for adrenal scanning and those used for the various established organ studies is reviewed. Radioactive gases are also discussed and tabulations are provided of the dose commitment to organs and tissues from ^{133}Xe. Although the need for microdosimetry was sometimes stressed, there was scant reference to work of this nature, and one suspects that the future sophistication of dosimetry will lie in this direction.

The volume contains certain papers which should be required reading for those working in the field of internal dosimetry. It also contains tabulations of specific absorbed fractions, mean dose per unit cumulated activity and other parameters which could be of value to those seeking to evaluate the dose in particular circumstances.

M. F. Cottrall.

1978, *British Journal of Radiology*, *51*, 328–332

Osteonecrosis in Hodgkin's disease

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ABSTRACT

Four patients suffering from Hodgkin's disease developed osteonecrosis following therapy and both femoral heads were involved in each case. Retrospective review of abdominal radiographs taken for follow-up lymphography demonstrated that the earliest radiological changes in bone were evident between five and 18 months after treatment was started and between six and 21 months before the onset of symptoms. The clinical implications are discussed.

Bone involvement is found in 5–10% of patients with Hodgkin's disease and may be lytic, sclerotic, or mixed in appearance. Osteonecrosis, or avascular necrosis, is not a recognized feature of this condition. The purpose of this communication is to report the occurrence of osteonecrosis in four patients following therapy and to emphasise that pain arising from osteonecrosis may be clinically confused with Hodgkin's infiltration of bone. The radiological findings are described and discussed in relation to treatment and onset of symptoms.

CLINICAL MATERIAL

This study was occasioned by the discovery of radiological changes of osteonecrosis in the hip of one patient who presented with pain following treatment for Stage III Hodgkin's disease. Subsequently three other patients presented in the same way. The clinical details of each patient are individually summarized, three patients receiving combination radiotherapy and chemotherapy, and one patient receiving chemotherapy alone. None gave a history nor had evidence of diabetes mellitus, gout, alcohol or drug abuse, dysbaric disease or previous relevant trauma. Abdominal radiographs taken at regular intervals following diagnosis were available in all four patients and these included the femoral heads in most instances. It was therefore possible, in retrospect, to analyse sequential radiological changes and to correlate these with the therapy regime and onset of symptoms.

CASE REPORTS

Case 1

A male aged 22, presented in January 1962, with night sweats and weight loss, generalized lymphadenopathy and hepatomegaly. Lymph-node biopsy showed nodular sclerosing Hodgkin's disease and he was clinically staged as IIIB. Single agent chemotherapy was commenced with Cyclophosphamide, followed by Vinblastine until in May 1965, he developed painful left inguinal lymphadenopathy. An applied dose of 1500 rad in seven fractions/12 days (max. bone dose: 1030 rad) was administered to a single small anterior field covering the left groin and including the proximal femoral head using a 6 MeV linear accelerator and he subsequently received further systemic therapy with Procarbazine. In January 1970, the development of enlarged tender nodes in the right inguinal region also required local irradiation (3500 rad applied in 12 fractions/16 days on ^{60}Co unit). The field again included the major part of the femoral head (max. bone dose: 2401 rad). Further chemotherapy was not given. However, in April 1971, his original symptoms returned and he was treated with six courses of MVPP* combination therapy and remained well until January 1973, when he complained of pain and stiffness of the right hip. Radiographs showed early changes of osteonecrosis in both femoral heads. On the right, progressive structural failure required the insertion of a low friction arthoplasty in June 1974. Histological examination of the excised bone showed no evidence of Hodgkin's disease. A full articular survey in August 1975 revealed unsuspected osteonecrosis in both humeral heads.

Case 2

A male aged 21, presented in February 1974, with malaise, weight loss and a swelling in the neck. Biopsy of a right supraclavicular node revealed Hodgkin's disease of a nodular sclerosing type which was staged IIIb disease following laparotomy and splenectomy. Between May and December 1974, he received six courses of MVPP chemotherapy. In May 1975, pain developed in the right hip region and there was radiological evidence of established osteonecrosis in both femoral heads.

Case 3

A 26-year-old male presented in November 1971, with a mass in the right side of the neck and frequent night sweats. Biopsy revealed nodular sclerosing Hodgkin's disease, classified Stage IIIb following laparatomy and splenectomy. In January 1972, treatment commenced with a course of the

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*MVPP—Mustine, Vinblastine, Procarbazine, Prednisolone.

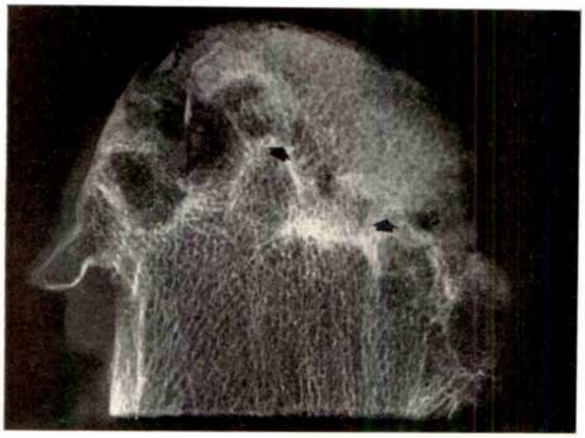

FIG. 1. *Case 3.*

Direct magnification radiograph of excised femoral head specimen. Articular collapse has occurred with the formation of a large dense subarticular osteonecrotic sequestrum. (▲) There is subjacent reactive cyst formation and sclerosis. Note the osteophyte arising from the medial articular margin and the periosteal thickening of the inner aspect of the femoral neck.

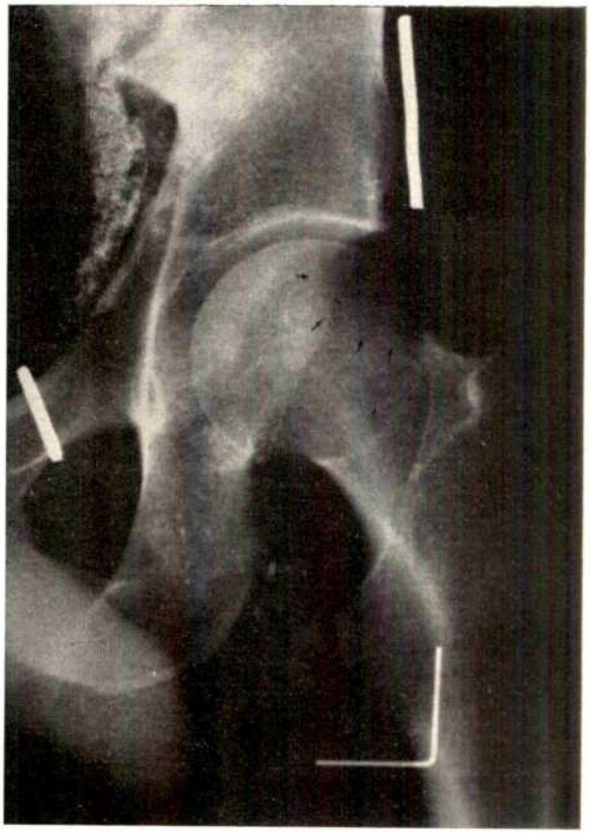

FIG. 2. *Case 3.*

Focal lesion—femoral head. There is a fairly well-defined crescentic area of bone destruction in the femoral head, as well as a little patchy sclerosis. (Planning film, prior to radiotherapy, but after chemotherapy.)

MVPP regime and was followed by total nodal irradiation* using a 15 MeV linear accelerator. A further five courses of MVPP commenced in September 1972 and the patient subsequently remained symptom-free for 18 months. He began to complain of right hip pain in April 1974, at which time both femoral heads showed radiographic changes of osteonecrosis. His symptoms progressed and in May 1977, he underwent a total hip replacement on the right side. Direct magnification radiography clearly demonstrates characteristic segmental collapse and sequestration (Fig. 1). Histological examination of the specimen showed no evidence of Hodgkin's disease in the femoral head.

Case 4

A male, aged 23, noticed a lump in the left side of the neck in June 1972. Cervical node biopsy at another hospital revealed nodular sclerosing Hodgkin's disease and the patient was referred for further investigation. Following laparatomy and splenectomy, this was pathologically staged IIIa disease. He was treated between January and April 1973, with total nodal irradiation and remained well until hilar lymph node recurrence and pulmonary involvement was observed on follow up chest X ray in January 1974. Treatment with six courses of MVPP resulted in complete disappearance of all detectable disease, until he complained of discomfort in the right hip in July 1975. Early changes of osteonecrosis were present in the right femoral head and in November 1975, a radiological survey revealed asymptomatic lesions in the left hip and right shoulder.

RADIOLOGICAL FINDINGS

Three types of radiological change were recorded and are classified according to the evolution of the disease.

Early focal lesion

The first radiological changes consisted of an ill-defined crescentic subarticular zone of rarefaction occupying the outer half of the femoral head (Fig. 2). This was accompanied by patchy dense mottling in the adjacent bone. The combination of irregular radiolucency and sclerosis was pronounced in two patients and the changes extended into the femoral neck region. Retrospective review of serial abdominal X-rays indicated that early focal lesions were apparent between six and 21 months before the onset of symptoms and between five and 18 months after the commencement of therapy.

Established subarticular lesion

This stage was identified by the formation of a discrete zone of rarefaction clearly demarcated by a thin sclerotic rim. In predominantly segmental lesions, the general configuration of the defect remains crescentic or ovoid in relation to the articular cortex (Fig. 3). Central lesions, however, occupy the

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*3500 rad MPD in 20 fractions/28 days to "mantle" field followed one month later by 3500 rad MPD in 20 fractions/28 days on "inverted Y".

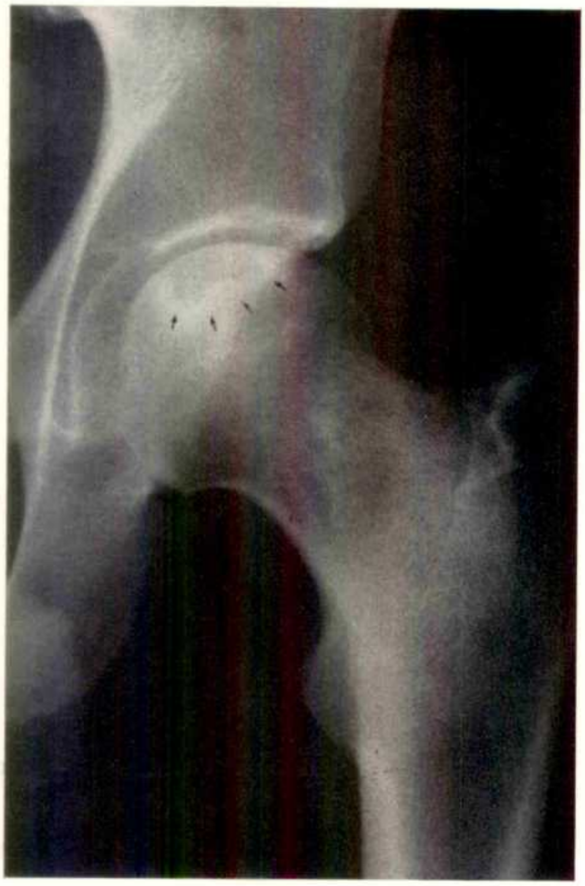

FIG. 3. *Case 1.*

Established lesion. A discrete zone of rarefaction has become demarcated by a marginal sclerotic rim (↑). Mixed radiolucent and sclerotic changes extend into the femoral neck. There is some acetabular rarefaction.

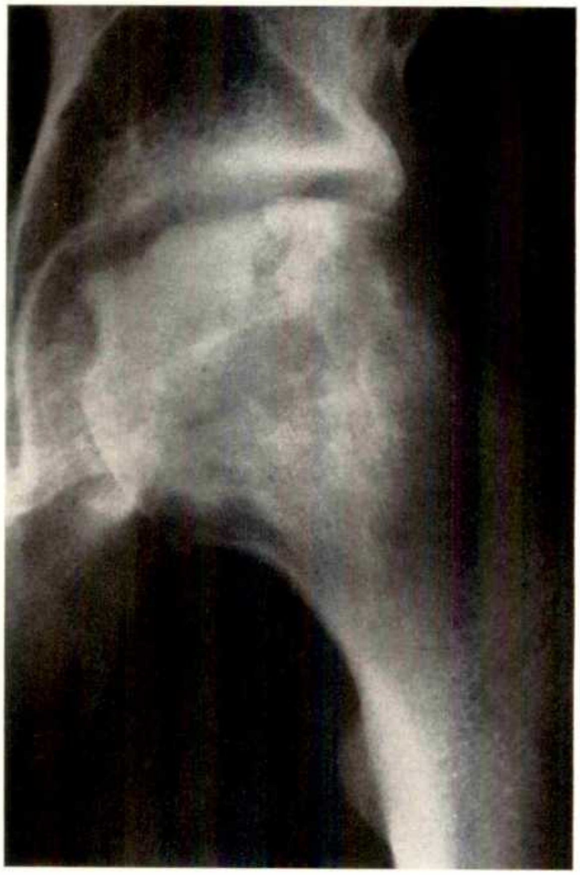

FIG. 4.

Articular collapse. Structural failure of subarticular bone results in collapse of the joint. Secondary joint deformity occurs with osteoarthrosis and periosteal buttressing of the inner margin of the femoral neck.

greater part of the femoral head, appear cystic and may contain dense amorphous calcification. These lesions were accompanied by reactive sclerotic changes in the adjacent femoral head or neck and variable acetabular rarefaction.

Articular collapse

At this stage, the lesion has progressed to structural failure of subarticular bone resulting in collapse of the joint. This was promptly accompanied by periosteal buttressing along the inner margin of the femoral neck (Fig. 4). Subsequent joint deformity invariably led to secondary osteoarthrosis necessitating surgical intervention in two patients.

DISCUSSION

Ihde and Devita (1975) have reported two patients with Hodgkin's disease and two with non-Hodgkin's lymphoma who developed osteonecrosis in the femoral heads following intensive combination chemotherapy which included the administration of intermittent corticosteroids.

A further four cases, all in patients with Hodgkin's disease, are now reported. In none of the patients has it been possible to establish a single clear aetiological relationship. In this respect, this resembles the condition of so-called spontaneous or idiopathic osteonecrosis of the femoral head (Patterson *et al.*, 1964; Merle D'Aubigné *et al.*, 1965).

The interval between the appearance of radiological changes and the onset of symptoms in this small group of patients is comparable to other types of osteonecrosis. In dysbaric osteonecrosis, it may be months or years after symptoms, before radiological signs develop, if at all (Davidson, 1976). It is of note that each of the four patients in this series had one symptomatic hip lesion and two had unsuspected shoulder involvement. Retrospective analysis of abdominal films in the four patients with Hodgkin's disease indicated that radiological signs were evident in the hips some six to 21 months before the onset of symptoms. A comparison was made of the temporal relationship between diagnosis of Hodgkin's disease, initiation of quadruple therapy and hip symptoms. The average interval between diagnosis and bone pain was 4.4 years and there was only 22.5 months separating the initiation of combined therapy and symptoms. It has not been possible to find any histological evidence of Hodgkin's disease in either of the two excised osteonecrotic femoral heads. This would suggest that the bone lesions are somehow related to the combined therapy rather than to Hodgkin's disease itself.

The occurrence of osteonecrosis in association with a variety of medical conditions for which high dose or intermittent steroid therapy has been used is well documented, but the exact role of corticosteroids in the production of bone damage is still controversial. The evidence is largely circumstantial and frequently conflicting (Murray, 1960; Velayos, 1966; Fisher *et al.*, 1969; McCollum *et al.*, 1970; Harrington *et al.*, 1971; Solomon 1973).

In case 3 early asymptomatic radiological changes were detectable in the femoral head within six months of the administration of a total dose of only 500 mg of Prednisone. It is perhaps reasonable to speculate that osteonecrosis occurs when a number of aetiological factors coincide in patients with particular vulnerability.

Certainly, each of these cases has stage III disease with a histological type (nodular sclerosing) which appears to have a predeliction for bony involvement. Each underwent bipedal lymphangiography as part of the pre-treatment assessment, but no signs of oil embolism could be found in the two femoral head specimens subjected to histological examination. Although three patients received radiation therapy to the regions of the hip joints (two as part of the total nodal irradiation and one to obtain control of local aggressive disease) treatments were applied using megavoltage beams which characteristically produce less preferential bone to soft tissue energy absorption when compared with orthovoltage beams. In no case could the dose absorbed by the femoral heads be considered to exceed the tissue tolerance of normal bone and it is now the policy in total nodal wide field irradiation to shield the regions of the femoral heads where possible while ensuring that all disease is encompassed. In his very large series of patients with Hodgkin's disease, Kaplan (1972) was able to record only one instance of pathological fracture following treatment by radiation therapy alone and in our case 1 the development of humeral head lesions was entirely unrelated to any local irradiation. We have observed no instances of bone necrosis in patients treated solely with cytotoxic agents and have found only one associated case reported in the literature. The suggestion, however, that corticosteroids are a contributing factor in the production of bone damage in what is a very small proportion of cases treated with combination chemotherapy is at present no indication to remove this drug from the present treatment schedules which have resulted in such a dramatic improvement in the quality of life and prospects for survival in patients with advanced or recurrent Hodgkin's disease. The British Lymphoma Investigation (1975) has reported a striking reduction in the complete remission rate from 80% with MVPP to 44% with MVP in Stage IV disease suggesting that Prednisone is a very important component of this schedule.

While it is rare for Hodgkin's disease to be complicated by bone necrosis, it seems likely that this association may occur more frequently than is at present clinically appreciated. In order to assess this, the routine abdominal follow-up lymphangiograms were examined in 100 random patients treated for Hodgkin's disease in this hospital. This has identified six with early signs of otherwise unsuspected osteonecrosis in the femoral heads and these patients will be closely followed for further developments. In conclusion, any patient who has received treatment either by chemotherapy or radiotherapy or a combination of the two and who complains of bone or joint pain, should be carefully screened for the characteristic signs of early osteonecrosis. If changes are suspected, an articular survey is indicated since any convex joint surface, in particular the shoulders and hips may be affected. In these patients it is important to distinguish osteonecrosis from malignant infiltration and thus avoid further potentially inappropriate therapy.

ACKNOWLEDGMENT

In reviewing this series we wish to thank Dr. A. M. Jelliffe of the Middlesex Hospital, for drawing our attention to another case. This was a young man with nodular sclerosing Hodgkin's disease, Stage III, who displayed similar radiological signs of osteonecrosis in the femoral heads as described.

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Book review

Lymphoreticular Disease. By I. Carr, B. W. Hancock, L. Henry and A. Milford Ward, pp. 214, 136 illus., 1977 (Blackwell Scientific Publications, Oxford, London, Edinburgh, Melbourne). £9·25 (Paperback.)

Presented as an introduction, this book covers in small compass the extending range of disorders of lymphoreticular tissues—from hypoplasia through hyperplasia to neoplasia. Leukaemias and tropical diseases are expressly excluded, although the former will often enter into the differential diagnosis of obscure lymphadenopathies, and in these days of commonplace air travel some knowledge of the latter in this context is essential. The emphasis is upon histopathology and the book will thus be of more value to the pathologist than to the clinician who is unlikely to have either time or material ever to become really familiar with the subtle changes seen in biopsy, surgical and autopsy specimens either by light or electron microscopy. Clear and concise textual descriptions cover the histology of a wide variety of lesions and are well illustrated in monochrome. It is however a pity that cytology is largely omitted, since in some instances, *e.g.*, myelomatosis, it can be of great practical value.

The introductory chapter defines the main cell types of lymphoreticular tissues—lymphocytes, plasma cells, reticulum and "reticular" cells and macrophages (histiocytes), describing their paraffin section morphology, ultrastructure and behaviour. Since recognition, sometimes enumeration of these various cells both in health and disease, likewise of certain pathological variants of unsure histogenesis, is fundamental to the whole diagnostic method, a comprehensive colour plate showing cytomorphology would have added much, although doubtless increasing the cost of production of the volume. Moreover, in describing architectural changes in lymphoid and related tissues, several simple line diagrams to illustrate their somewhat complicated micro-anatomy would have been most helpful.

The majority of morbid anatomists would agree that possibly the most difficult area in diagnostic histopathology is the lymph-node biopsy; hence the paramount need to understand the topographical structure of lymphoid tissues and this cyto-analytical method of study which leads to rational diagnostic synthesis. The well written textual descriptions give ample warning of difficulties of interpretation of observed changes, whether by light or electron microscopy. Nevertheless one feels the need for a further chapter in which the natural sequences of histological diagnosis are more closely followed to a decision tree which may lead to firm diagnosis, to a differential listing or a recommendation for other investigations. The broader aspects of investigational tactics are well covered in Chapter 11 (Investigation & Management), but not the analytical approach required by the histologist except in respect of malignancy or otherwise.

The classification and staging of lymphoreticular disorders are well described and discussed and a useful section deals briefly with the essentials of other appropriate investigations—haematology, biochemistry, immunology and various radiodiagnostic procedures, the latter with some stress on isotope scanning and lymphography. These sections will perhaps prompt the interested reader to turn elsewhere for amplification, a similar comment also applying to the still advancing subject of treatment.

Good descriptions are included of thymic, splenic and hepatic disease, the latter being particularly relevant to the process of staging as now practised for Hodgkin's disease. There is also a short but practical appendix on technical methods for the pathologist and electron microscopist.

In summary, this book is excellent value and well produced with an extensive bibliography and adequate subject index. It certainly covers the subject well despite its brevity.

C. H. G. PRICE.

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Needle aspiration/biopsy of the spine in suspected disc space infection

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Abstract

Closed needle aspiration/biopsy was performed in 19 patients with suspected spinal disc space infection. A precise diagnosis was made from the material obtained in 13 (68%); the infecting organism was isolated in 11 and malignant tumour diagnosed histologically in two. There were no important complications. The procedure which is described in detail is simple to perform and can be carried out early in the course of a patient's stay in hospital, thereby enabling prompt treatment.

The diagnosis of disc space infection can be difficult and is often delayed. Appropriate antibiotic therapy depends on identifying the pathogenic bacteria. Needle aspiration/biopsy is a simple, reasonably effective and safe method of obtaining material from the infected disc and adjacent vertebrae. We wish to present our experience in using the technique in 19 patients with suspected disc space infection.

Materials and Methods

All 19 patients included in this report were referred for needle aspiration/biopsy because of suspected disc space infection.

They presented with the following features:

(1) *Back pain* which had been present for 1–11 months before biopsy. None of the patients had, as far as is known, been given antibiotics.

(2) *Localized radiological abnormality showing:*

(a) disc space narrowing

TABLE I

Clinical and pathological details

Case No.	1	2	3	4	5	6	7	8	9	10
Age	56	4.5	68	51	20	68	64	60	68	87
ESR	↑	↑	↑	↑	↑	N	↑	N	↑	N
WBC	↑	↑	↑	N	↑	N	↑	N	↑	N
Temp.	↑	N	N	N	↑	↑	↑	N	N	N
Culture	St.	TB	St.	TB	TB	Stp.A	Stp.A	St.	Stp.A	St.
Histology	T	—	N	—	—	—	Inflamm.	N Bone	Inflamm.	Bone

Case No.	11	12	13	14	15	16	17	18	19
Age	21	45	28	75	69	63	16	50	36
ESR	↑	↑	↑	↑	↑	↑	↑	↑	↑
WBC	↑	↑	N	↑	↑	N	N	N	N
Temp.	↑	↑	N	N	↑	↑	N	N	N
Culture	St.	TB	Stp. A	St.	Stp.A	St.	St.	Stp.A	E.coli
Histology	T	—	—	Inflamm.	—	Inflamm.	Inflamm.	—	—

Stp.A = Staph. aureus
St. = Sterile
↑ = Increased
N = Normal
T = Tumour
Inflamm. = Inflammatory tissue, non specific

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(b) bone destruction on one or both sides of the disc.

(3) *A clinical suspicion* by the referring orthopaedic surgeon or rheumatologist that infection was present.

Between 1970 and 1977 22 patients fulfilled these criteria. In 19 records were adequate. In three patients records were inadequate and these are not included in this report (organisms were obtained in two of these patients so their exclusion does not give an advantageous bias to the figures presented).

The age range was from 4.5–87 years with a mean of 47 years. Eight cases were male and 11 cases were female.

The levels of the lesions in the spine and their nature are shown in the histogram. Relevant clinical and pathological details are shown in Table I.

TECHNIQUE

The aim is to introduce a needle into the area suspected of being diseased. It is sometimes possible to aspirate pus through an ordinary needle; we use a 14 cm 18 gauge translumbar aortogram needle. Friable bone can also be sucked into such a needle and then be expelled with a trocar, but in many instances a trephine biopsy is required. Even if pus is present it may not be possible to reach it without cutting a "window" through the overlying bone. Needles capable of cutting through the bone of the vertebral body have been described by Ackerman (1956) and Craig (1956). We use the Ackerman Instrument (Becton Dickinson) with which a core 1.5 mm in diameter can be obtained. The component parts are illustrated in Figs. 1 and 2.

In the lumbar region the needles are introduced through the muscles of the back along a course that avoids the transverse processes of the vertebrae and the kidneys to reach the postero-lateral aspect of the vertebral body as shown in Fig. 3.

The procedure can be performed under local anaesthesia; we have used Pethidine as a premedication and Xylocaine 2% to the periosteum for local

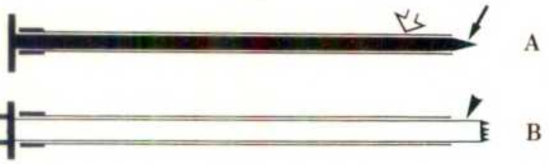

FIG. 1.

(A) The Ackermann needle comprises a trocar (closed arrow) and cannula (open arrow).

(B) When the trocar has been removed the trephine (arrow head) is inserted.

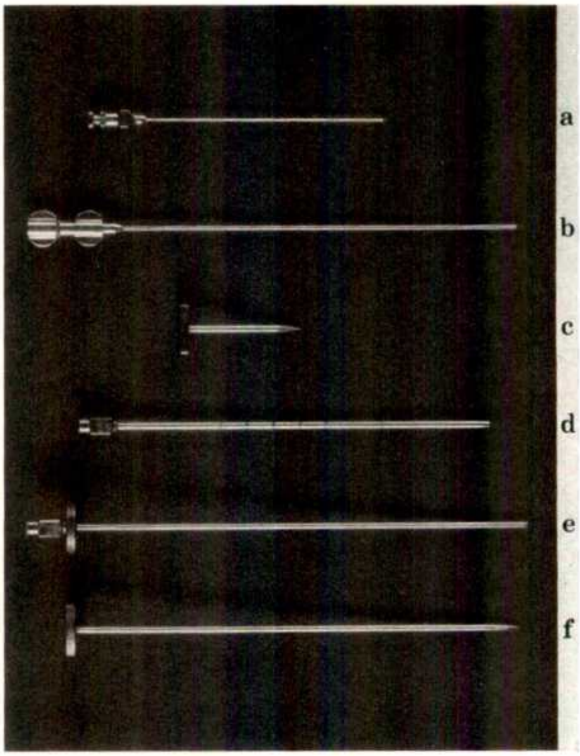

FIG. 2.

The needles used in aspiration/biopsy. Local anaesthetic is injected via the 23 gauge spinal needle (a) and aspiration is attempted with the 18 gauge translumbar needle (b). Before biopsy the skin is punctured with the perforator (c), followed by the cannula (d) plus trocar (f). The trocar is then replaced by the trephine (e).

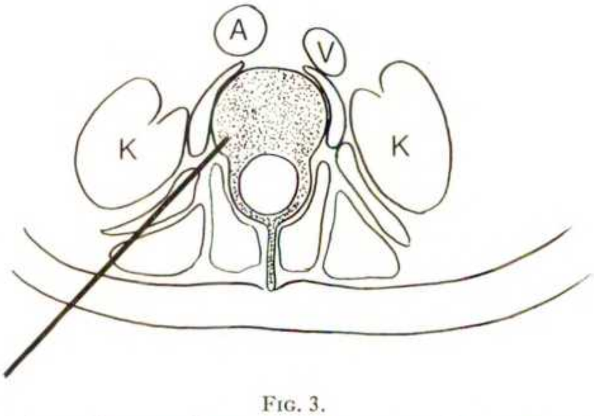

FIG. 3.

The needle enters the postero-lateral aspect of the vertebral body, thus ensuring a long intra-osseous course. The relationship to the aorta (A), inferior vena cava (V) and kidneys (K) is shown.

anaesthesia. If the patient's back is tender local anaesthesia is usually insufficient to prevent considerable pain as the needle nears the site of pathology. Most patients with infection have local tenderness and we now use general anaesthesia in all cases of suspected infection.

The patient lies prone on the X-ray table under a standard vertically orientated image intensifier. Horizontal screening is a considerable advantage over films for the control of the lateral projection. With it, the whole procedure can be accomplished in 10–20 minutes. We use a portable 17 cm image intensifier aligned horizontally (Siemens Siromobile 2). If the patient is at the centre of both beams access for the operator becomes difficult, so we offset the portable machine and simply move the floating table top on which the patient is positioned to achieve optimum centring.

The skin of the back is prepared as for surgery. The point of entry of the needle is 7–9 cm from the mid-line for lumbar discs, and 6–7 cm in the thoracic region. The level, decided at fluoroscopy, is chosen so that the needle will reach the affected area without hitting transverse processes or ribs. The approximate angle of entry is 45 deg. To sample material from the L5/S1 disc or lower half of L5, the needle needs to be angled caudad from a point above the iliac crest to pass below the transverse process of L5. This is one of the most difficult sites to biopsy as the pathway is so limited. Before passing the trephine instrument, a 23 gauge spinal needle is passed down to the periosteum of the postero-lateral portion of the disc or vertebral body to be sampled. This needle can be used for injecting local anaesthetic. Using the biplane screening the needle tip can be accurately positioned. A perforation is made in the skin and underlying fascia with the skin perforator. Puncturing the skin with the perforator is necessary because the tip of the trocar is deliberately blunted so that, according to Ackerman (1956), "it can advance through muscles and thin fasciae, but not through nerves or blood vessels, which are not injured by the non-cutting instruments if limited force is applied". The trephine guide (trocar) with its outer closely fitted cannula (Fig. 4) is then passed along the same path (the fine needle may be left in place and the trocar/cannula combination passed alongside it). It is easy to feel when the point of the trocar hits the bone or the ligaments surrounding the disc. This is checked in both planes by screening. The outer cannula is then advanced over the trocar using a rotary movement until it is observed to cover the tip. The trocar is removed and the trephine, which has serrations which cut when rotated clockwise, can now be passed through the cannula to cut into the bone or disc (Fig. 5). Suction is applied to the trephine needle as it is advanced with clockwise rotation. A vigorous twist is made just before

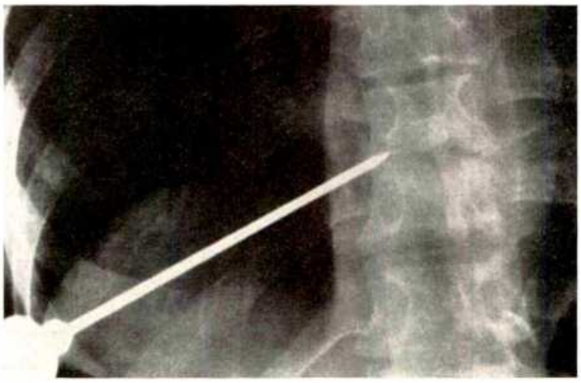

FIG. 4.

The trocar and cannula in contact with the postero-lateral aspect of the vertebral body.

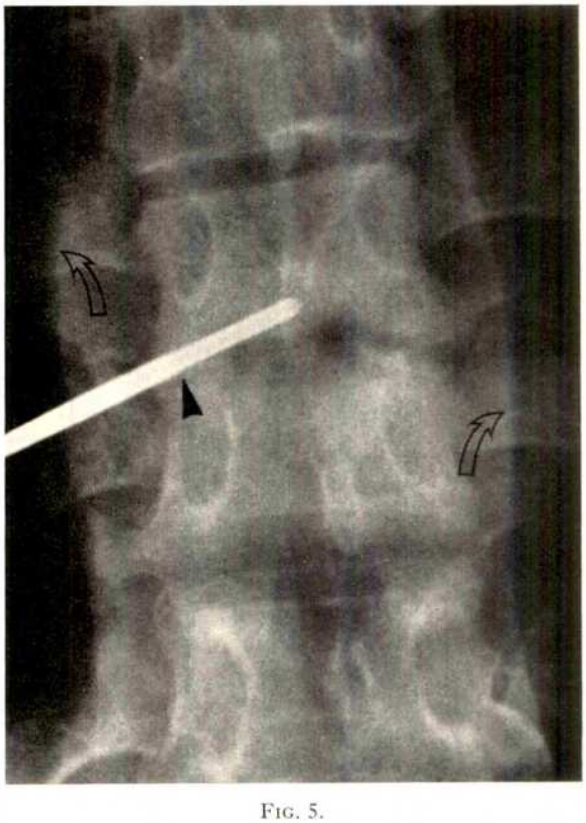

FIG. 5.

The trocar has been replaced by the trephine which projects beyond the end of the cannula (arrow head) into the vertebral body. Note the reduced joint space and paravertebral soft tissue mass (open arrows).

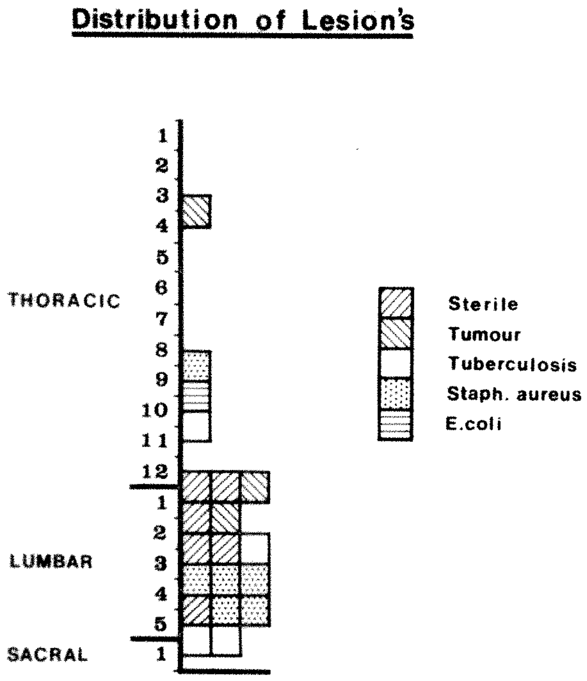

FIG. 6.

Note that two disc spaces were involved in one patient with tumour. In all the other patients only one space was affected.

withdrawing the specimen in order to ensure that the core breaks free. Once a small window has been cut in the cortex the passage of the trephine becomes easier. The longer trephine is 4 cm longer than the cannula and specimens can be obtained across the full diameter of the vertebral body. Care is taken not to pierce the front of the vertebral body as the aorta and the inferior vena cava are in close proximity. If the initial cannula position is on the lateral aspect of the vertebral body there is less bone for the trephine to traverse, so the postero-lateral site is usually preferable.

It has been our practice in patients with suspected disc space infection to obtain samples from the affected disc and from the abnormal bone in the adjacent vertebrae, but if pus is aspirated we stop, because so far all samples containing pus have grown pathogenic organisms. We have found that even if the disc is substantially narrowed it may occasionally only be possible to find pus in the adjoining vertebrae.

Once the needle is removed, a small dressing for the puncture point is all that is required.

RESULTS

In five patients (26%) the disc space was entirely lost; organisms were cultured in three of these patients. In the remaining 14 the disc space was reduced; organisms were cultured in eight and tumour diagnosed in two.

Pus was obtained in eight patients (42%) and the organism was grown on each occasion, three cases being *Mycobacterium tuberculosis*, four being *Staphylococcus aureus*, and one being *Escherichia coli*. We drained 135 ml of pus from one unsuspected tuberculous abscess and the extent of the cavity was demonstrated by the injection of water soluble contrast medium. Friable bone was obtained in four patients (21%), one being tumour, one growing *Mycobacterium tuberculosis*, one growing *Staphylococcus aureus*, and one being sterile. Macroscopically normal bone, as judged by the operator, was obtained in seven (37%) and of these five were sterile, one grew *Staphylococcus aureus* and one was tumour.

In 13 patients (68%) the diagnosis was established (11 infections and two tumours). In the remaining six the procedure was unhelpful.

The outcome of the patients on follow-up for one to five years is as follows:

(1) The 11 patients in whom an organism were cultured were treated appropriately and all improved.

(2) Both patients with malignant disease subsequently died; the diagnoses were confirmed at autopsy.

(3) Six patients had sterile cultures and no malignancy on histology. In two of these the clinical and radiological diagnosis was of tuberculosis and so despite the negative culture they were given antituberculous therapy and improved clinically. The histology was of non-specific inflammatory tissue. One was given a course of antibiotics but was lost to follow-up. One was given no treatment, clinically did not change and is thought to have degenerative disease. Two others were not treated and were lost to follow-up. Radiologically they were also probably degenerative disease.

COMPLICATIONS

In one case a tuberculous abscess formed in the soft tissues along the needle track. This patient had at least one unsuspected paraspinal abscess prior to needling, and the extra one made little difference to his management. The patient with *E. coli* disc infection developed pneumonia following a biopsy of T9/10. This patient had a small pneumothorax following the procedure and the pneumonia appears to have developed in the lung traversed by the needle.

DISCUSSION

An accurate diagnosis in patients suspected on clinical and radiological grounds to have spinal infection is often difficult. Laboratory investigations do not always provide the answer; the leucocyte count and E.S.R. may be normal (Harris and Kirkaldy-Willis, 1965; Kemp *et al.*, 1973a). Staphylococcal anti-alpha-haemolysin and anti-Panton Valentine leucocidin titres cannot be assayed universally and were positive in only three of the five cases of proven *Staph. pyogenes* infection in the series reported by Kemp *et al.* (1973b), but in ten out of 94 of their patients with proven tuberculosis there was significant elevation of one or both of these antibodies, *i.e.* a false positive result. Even in those cases where there is little doubt regarding the presence of disc space infection, optimal treatment depends on isolating the infecting organism. Blood cultures are positive in one quarter or less of patients with pyogenic infection (Ambrose *et al.*, 1966; Garcia and Grantham, 1960; Griffiths and Jones, 1971).

In many patients absolute proof of infection and subsequently the sensitivities of the organisms to antibiotics depends on culturing material obtained directly from the infected disc or bone. Biopsy during surgery for paraparesis, the prevention of deformity, or the drainage of abscesses is one method, but open surgical biopsy is also undertaken for purely diagnostic purposes (Kersley, 1977). Isolation of the organism at open operation was achieved in 73% of tuberculous infection (Kemp *et al.*, 1973b).

Needle aspiration/biopsy in our series provided a positive diagnostic yield in 13 of the 19 patients (68%). In 11 the infecting organism was cultured, in two tumour was diagnosed on histology. Ambrose (1966) obtained the infecting organism in eight out of 16 patients with pyogenic infection and Garcia (1960) in five out of ten such patients. Clearly, lower success rates will be achieved in patients who have received antibiotic therapy prior to needling. Since material is also obtained for histology, it is possible to confirm the diagnosis of infection in at least some of the patients in whom it proves impossible to isolate the organism.

As with all needle biopsy techniques spinal needle aspiration/biopsy cannot be relied upon to exclude pathology. In six of our patients the technique was classified as unhelpful in that we failed to grow an organism and no tumour was found on histology. Two of these were almost certainly infection, as in these two histology showed inflammation.

The complication rate is very low. One of our patients developed an abscess along the needle track but as he already had tuberculous paraspinal abscesses the extra one did not materially affect his management. A second patient developed pneumonia following biopsy of a thoracic disc space which cleared rapidly on treatment. Except in these patients there was no post-procedure discomfort, and the patients had no symptoms to suggest to them that anything had been done to their back.

Since needle aspiration/biopsy is a comparatively minor procedure and requires only 30 minutes in an X-ray room (providing screening in two planes is feasible), it can be undertaken concurrently with other tests rather than waiting until all investigations are completed, as is often the case with open surgery. Needle aspiration/biopsy, if positive, may avoid open surgery which is a major procedure when the prime object is to obtain material for diagnosis. We would therefore recommend that it should be undertaken early in the course of the patient's investigation, except where urgent surgery is required for other reasons.

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The metacarpal index in Jamaican children and adults

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ABSTRACT

The metacarpal index was measured in radiographs of the hands of 615 male and 667 female Jamaicans aged over two years. The index increased with age from two years to adulthood, and was greater in females than in males, and greater in the left hand than the right hand. Means and standard deviations of the index for the left hand are presented as standards. An index of 9.6 for males and 10.1 for females over the age of 13 years is suggested as the upper limit of normal (three standard deviations above the mean). These standards are higher than those previously reported, and are probably applicable to other black populations outside Jamaica.

The metacarpal index (MCI) has been used in the assessment of arachnodactyly since the technique of its measurement was described in 1960 (Sinclair *et al.*). In succeeding years Parish (1960, 1966, 1967) produced tables giving means and standard deviations separately for 133 British men and women between the ages of 21 and 45 years, and his upper limit of three standard deviations above the mean has come to be accepted as the separation between normal and arachnodactyly (Lusted and Keats, 1972).

In 1969 Joseph and Meadow published figures for 50 British infants up to the age of two years, but there have been no reports of the MCI between the ages of two and 21 years.

During routine reading of hand X-rays of Jamaicans, who are predominantly of African origin, it appeared that many apparently normal subjects had long, slender fingers. If it is presumed that Parish's subjects were white, then no studies have been published on the MCI in blacks, apart from a few cases mentioned by Eldridge (1964). The aim of this investigation was to establish the normal range of the MCI in Jamaican children and adults.

SUBJECTS

The MCI was measured in 1282 hands in two groups of subjects. The first group was of 400 hand X-rays drawn from the files of casualty films in the University Hospital of the West Indies. The films were selected only so far as to ensure that the subject was 20 years old or over, and that there was no evidence on the X-ray of any metacarpal abnormality. The oldest subject was 89 years, and 42% were between the ages of 20 and 29 years. There were 100 X-rays each of male left, male right, female left and female right hands. No information was available on the height of the subjects, nor on the presence of disease other than in the hand.

The second group of 882 radiographs were from subjects living in the rural Jamaican district of Lawrence Tavern. Those aged two to four years were X-rayed in 1966, and were the subject of longitudinal investigations of child development (Standard *et al.*, 1969). Children from seven to 16 years attending a primary school in the same area

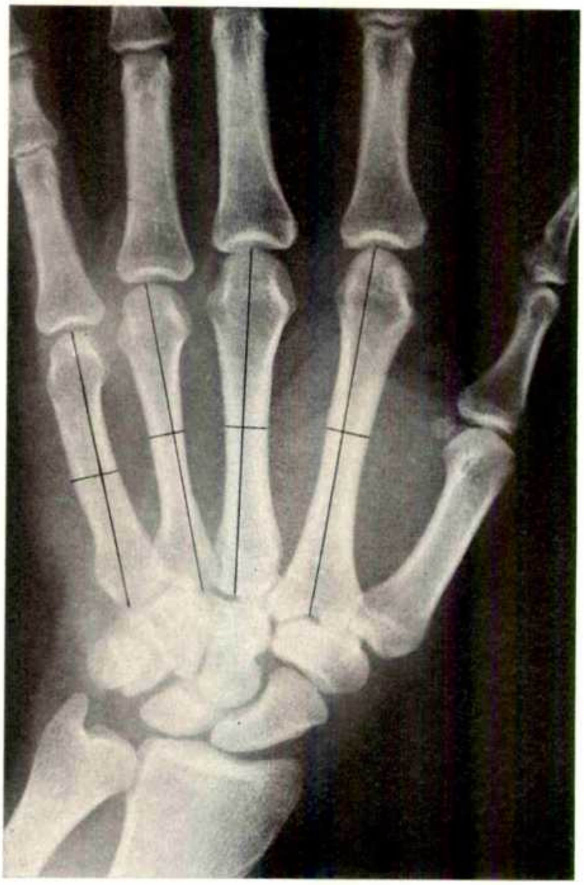

FIG. 1.

Radiograph of a hand showing how the length and width of each metacarpal was measured.

TABLE I

THE METACARPAL INDEX IN ADULTS OVER 20 YEARS

Males	Number of subjects	Mean metacarpal index	Standard deviation	Range
Left hand	100	7.88	0.58	6.67–9.96
Right hand	100	7.53	0.58	6.28–9.42
Females				
Left hand	100	8.17	0.64	6.43–9.95
Right hand	100	8.09	0.60	6.77–9.46

TABLE II

THE METACARPAL INDEX OF MALES AGED TWO TO 20 YEARS

Age	Number of subjects	Metacarpal Index			Height		Correlation coefficient of MCI/height
		Mean	Standard deviation	Range	Mean	Standard deviation	
2–	30	6.05	0.55	4.81–6.98	89.3	4.5	+.31
3–	70	6.26	0.56	4.79–7.52	93.9	5.4	+.11
4–	11	6.81	0.74	6.09–8.41	98.2	4.7	0.00
7–	19	7.11	0.65	5.97–8.60	120.3	3.6	+.13
8–	40	7.29	0.65	6.15–8.76	124.3	6.1	+.10
9–	57	7.29	0.60	6.26–8.85	127.5	5.7	0.00
10–	37	7.26	0.63	6.12–8.77	133.5	6.1	+.10
11–	47	7.53	0.74	6.39–8.69	138.7	6.4	+.19
12–	25	7.49	0.62	5.99–8.17	140.7	6.1	−.16
13–	20	7.57	0.63	6.10–9.02	146.7	8.6	−.13
14–	17	7.75	0.54	6.69–8.53	148.7	7.5	+.48
15–	13	7.66	0.92	6.27–8.95	157.1	9.3	+.34
16–	5	7.53	0.57	6.72–8.10	160.5	2.0	+.75
17–	13	8.00	0.78	6.38–9.29	170.2	5.0	0.00
18–20	11	8.02	0.64	6.99–9.16	165.4	7.1	+.23

TABLE III

THE METACARPAL INDEX OF FEMALES AGED TWO TO 20 YEARS

Age	Number of subjects	Metacarpal Index			Height		Correlation coefficient of MCI/height
		Mean	Standard deviation	Range	Mean	Standard deviation	
2–	42	6.44	0.62	4.82–7.75	88.9	4.4	+.24
3–	86	6.68	0.79	4.73–7.98	93.5	4.9	+.18
4–	16	7.24	0.70	6.34–8.15	104.0	5.0	+.34
7–	29	7.43	0.78	6.07–8.91	120.4	5.2	+.36
8–	27	7.59	0.65	6.35–8.63	125.4	5.9	−.01
9–	41	7.47	0.75	6.03–8.80	128.4	6.3	+.22
10–	43	7.85	0.80	6.17–10.52	135.7	7.3	+.29
11–	41	7.89	0.76	6.42–9.39	138.9	5.8	+.08
12–	36	7.99	0.64	6.87–9.35	145.7	8.4	−.20
13–	22	8.07	0.67	6.64–10.27	151.3	6.5	+.33
14–	18	8.52	0.75	6.92–9.75	154.9	4.0	+.07
15–	17	8.05	0.72	6.89–8.85	157.2	6.1	+.08
16–	18	8.43	0.55	7.85–9.36	156.8	7.3	+.17
17–	17	8.30	0.54	7.56–9.56	159.7	5.2	+.44
18–20	14	8.58	0.54	7.58–9.61	160.0	4.7	+.25

were X-rayed in 1967; the skeletal maturation of the hand and wrist of these groups of children was reported by Marshall *et al.* (1970). An older group of children from a neighbouring secondary school and other subjects under 20 years living in the vicinity were X-rayed in 1970. These, together with those primary schoolchildren who were older than 12 years were used as controls for a study of the skeletal age of Jamaican adolescents with sickle cell anaemia (Ashcroft *et al.*, 1972). Height was measured at the same time as the radiograph was taken, except for a few of the younger children for whom it was obtained by interpolation from growth charts. In all these children, X-rays of the left hand and wrist were taken, using non-screen film with the tube centred above the head of the third metacarpal at a distance of 76 cm.

METHODS

The technique used for measuring the MCI differed slightly from that of Parish (1966). His method of dividing the metacarpals axially into two equal halves by eye is open to considerable observer error. In the present study, the axial length of the second and third metacarpals was measured from the tip of the metacarpal head to the apex of the notch at the base. For the fourth and fifth metacarpals, the length was taken as the longest distance from the tip of the head to the most proximal part of the base (Fig. 1). When compared to Parish's method, the lengths of the second and third metacarpals measured by the present technique are slightly shorter, but those of the fourth and fifth may be slightly longer. The width of each metacarpal was determined at the exact midpoint of its measured length. Lengths were recorded to the nearest one millimetre, and widths to the nearest half millimetre.

The relative slenderness of each metacarpal is the ratio of the length to the width; the MCI is then calculated as the mean relative slenderness of the second to fifth metacarpals (Sinclair *et al.*, 1960; Parish, 1960, 1966, 1967; Eldridge, 1964; Joseph and Meadow, 1969).

RESULTS

The mean MCI, standard deviation and range for each sex and hand of adults over 20 years is shown in Table I. For both sexes, the index for the left hand was higher than the right, a significant difference in males ($t=4.39$, $p<0.001$) but not in females ($t=0.84$, $p>0.1$). Indices for females were higher in both hands than for males, and both of these differences are significant (left hands: $t=3.08$, $p<0.01$; right hands: $t=6.71$, $p<0.001$).

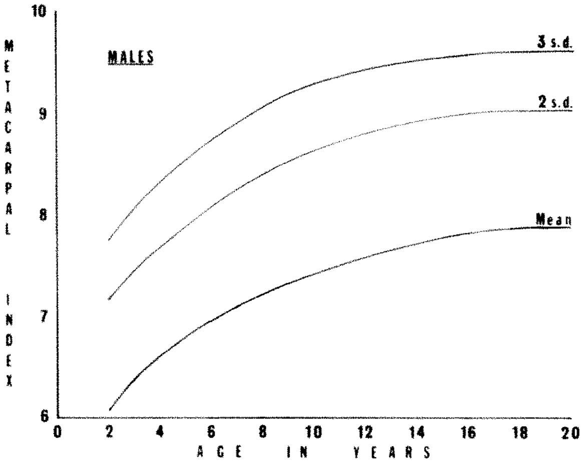

FIG. 2.

Mean and standard deviation (SD) curves of the metacarpal index in males.

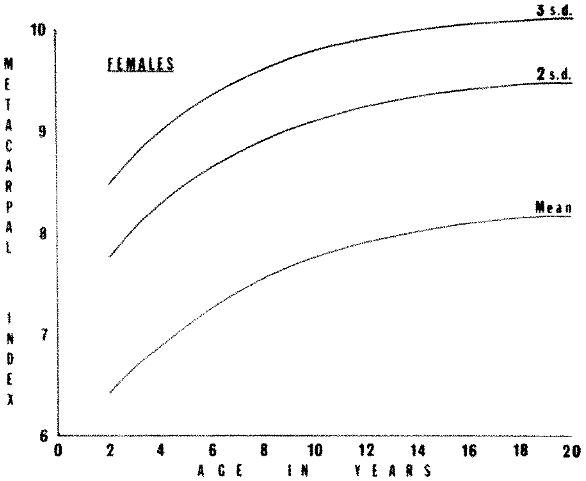

FIG. 3.

Mean and standard deviation (SD) curves of the metacarpal index in females.

The mean MCI, standard deviation and range, mean height, and correlation coefficient for MCI against height is shown in Tables II and III for children from ages two to 20 years. Only in one age group (14 year old males) was the MCI/height correlation significant at the 5% level; at all other ages there was no significant correlation, although the coefficient was positive at the majority of ages.

Figures 2 and 3 show that the mean MCI rises from two years; the rise is at first relatively steep, but after about 13 years the MCI changes little.

DISCUSSION

The MCI is a useful clinical measurement for the diagnosis of Marfan's syndrome and other causes of arachnodactyly. The indices of patients with these conditions have been shown to be higher than normal, although Parish (1967) noted that the slenderness of the fingers might be due to the shape of the phalanges more than that of the metacarpals. It must be remembered, however, that the diagnosis of Marfan's syndrome also depends on other signs, including the ratio of sitting to standing height, other skeletal disorders, ocular and cardiovascular features.

The results show that when using the MCI, allowance must be made for age, sex, ethnic origin, and whether the radiograph is of the left or right hand.

Tables II and III and Figs. 2 and 3 show that the MCI of the left hand increases from about 6.0 to 8.0 in males, and from about 6.4 to 8.4 in females, from the age of two years to adult life. One cause of this increase may be related to epiphyseal ossification; the metacarpal epiphysis of infants is not ossified, and the MCI can therefore be calculated from the metaphysis and diaphysis only. The MCI of subjects under two years (Joseph and Meadow, 1969) has been found to be considerably lower than that of Jamaican children aged two years whose MCI was only calculated if epiphyseal ossification had begun. With growth, the size of the ossified epiphysis approaches that of the adult metacarpal, so that the measured length increases more than the width. By about 13 years, the radiological width of the metacarpo-phalangeal joint has decreased to adult proportions, and subsequently changes little (Greulich and Pyle, 1966).

The absence of significant correlation between height and MCI within early age groups suggests that the MCI is not directly related to height, but rather to age, and probably to skeletal maturation. Eldridge (1964) also found that in tall subjects the MCI was not significantly greater than in those of average height.

The mean MCI of the left hand was 0.33 greater than that of the right hand in men (a significant difference), and 0.08 in women (not significant). This agrees with the findings of Parish (1966). Radiographs of the children had been taken of the left hand only, and therefore standards are presented based on the left hand.

The mean MCI of Jamaican adults was higher than those of British adults examined by Parish (1966), who found values in the left hand of 7.02 in men and 7.78 in women, and in the right hand of 6.86 in men and 7.60 in women. These differences are probably due to the ethnic origins of the subjects, those in Jamaica being predominantly black, and those measured by Parish presumably predominantly white. Further work is needed to investigate the ethnic difference in the metacarpal index.

Figures 2 and 3 show the smoothed curves of the mean and two and three standard deviations above the mean for the MCI of the left hand of Jamaicans from two years to adulthood. These curves can be used as standards for the normal Jamaican population. If a limit of three standard deviations is accepted as being the upper limit of normal, then arachnodactyly in Jamaicans is suggested by values of the MCI of the left hand above 9.62 in males and 10.09 in females. In order to simplify this arbitrary classification, values of above 9.6 in males and above 10.1 in females could be taken as the upper limits of normal for all Jamaicans over the age of 13 years. These standards are likely to apply also to other black populations.

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The appearances of renal transplant lymphocoeles during dynamic renal scintigraphy

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Abstract

Eight patients are described in whom transplant lymphocoeles were drained. All had ^{99}Tc^m-DTPA dynamic renal scintigrams performed pre-operatively; five showed features of obstruction. Photon deficient areas on the scintigrams and bladder deformities were of particular value in detecting lymphocoeles.

Perirenal collections of lymph are a recognized, though not common, complication of renal transplantation (Inocencio *et al.*, 1969; Koehler and Kyaw, 1972; Madura *et al.*, 1970). Braun *et al.* (1973) reported on 15 cases and reviewed the literature. They postulated a number of potential causes of formation of lymphocoeles, including rejection, potent diuretics, steroid therapy and surgical division of the lymphatics of the allograft. Diagnosis may be obvious clinically, with a palpable mass, swelling of the leg on the side of the transplant and obstruction of the ureter. The latter may be detected clinically or noted on routine investigation of transplant function.

In our department, sequential studies of renal transplant function are carried out using ^{99}Tc^m Diethylenetriaminepentaacetic Acid (DTPA) for the early detection of rejection (Hilson *et al.*, 1977). The first study is usually performed within 24 hours of transplantation and then at frequent intervals thereafter. During the last three years, over 1600 studies with DTPA have been carried out on 202 transplanted patients. We describe the appearances of eight patients with post-operative lymphocoeles.

Materials and Methods

Sequential imaging of patients following the bolus injection of 555 MBq (15 mCi) of DTPA was carried out using either an Ohio Nuclear series 100 or 110 gamma camera positioned anteriorly over the transplant. Serial images were recorded on Polaroid or 10 in. × 8 in. nuclear medicine film (Kodak) for the first 30 seconds following injection, then at 2, 5, 15 and 30 minutes with a final bladder image. The two minute image comprised 300 000 counts and the later images were acquired in the same time as that

TABLE I

Salient features of transplanted patients

Patient	Sex	Age	Donor C=Cadaver R=Related	Time of diagnosis after transplantation (weeks)	Number of major rejection episodes	Clinically silent	Confirmation preoperatively ND=not done		Pre-operative evidence of obstruction	Approx. volume (ml)
							IVU	U/S		
N.B.	M	22	R	40	2	no	+	ND	+	250
J.W.	F	25	C	12	4	no	−	+	+	500
R.W.	M	25	C	4	2	yes	−	+	+	800
J.R.	F	10	C	21	4	yes	+	+	+	250
M.B.	M	14	C	4	0	yes	+	ND	−	200
J.G.	M	37	C	3	2	no	+	ND	−	400
L.R.	M	60	C	22	5	no	+	ND	+	1500
H.F.	M	28	R	37	1	no	−	ND	+	1000

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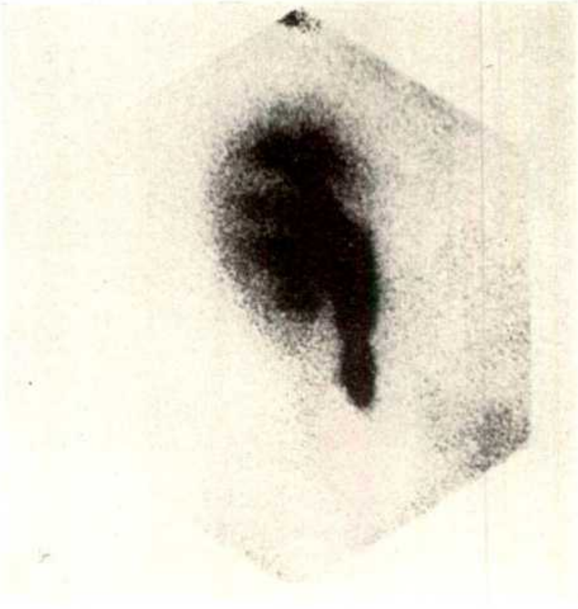

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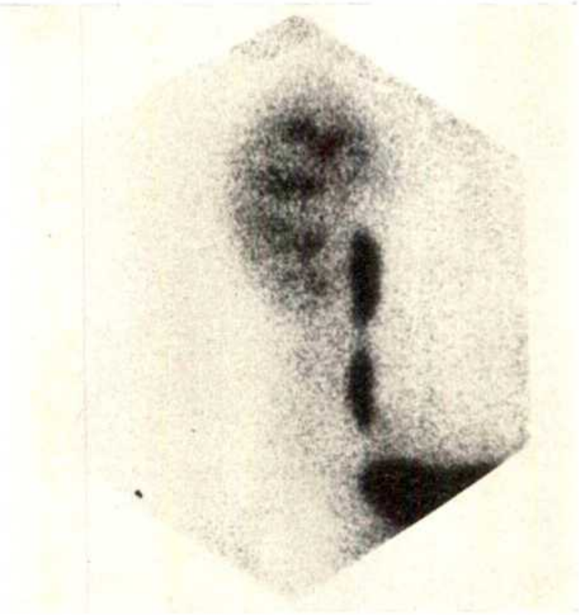

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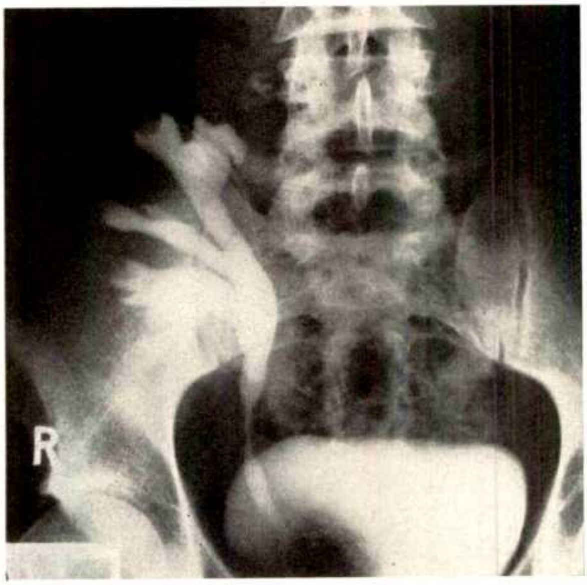
FIG. 1. (N.B.)

(C) Post-operative 15-minute image showing no hold up of tracer and resolution of the photon deficient lymphocoele seen in Fig. 1A.



B

FIG. 1. (N.B.)

(A) Fifteen-minute image showing the photon deficient lymphocoele at the lower end of the ureter.

(B) IVU showing ureteric narrowing due to the lymphocoele.

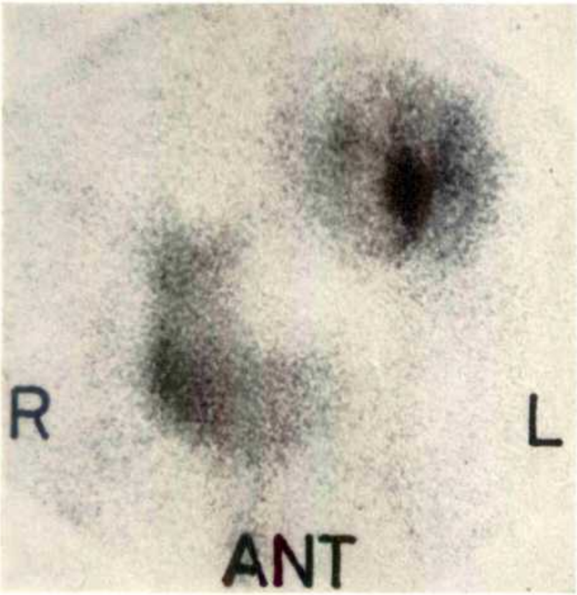
for the two minute image. Data were simultaneously recorded in a PDP 11 dedicated minicomputer (DEC Gamma 11) for the later analysis. In some patients, images at two hours or later after injection were recorded, with lateral views for further definition of the bladder and the lymphocoele.

CASE REPORTS

The salient features of the eight patients are shown in Table I. The diagnosis of a lymphocoele was made, on average, 18 weeks after transplantation, though this varied from three to 40 weeks. All the patients were treated with prednisolone and azathioprine, initially at high doses which were then gradually reduced. During acute rejection phases, 1 g of methyl-prednisolone daily was given for three days with, in some patients, actinomycin D and radiotherapy. All also received therapy with frusemide at some time in their post-operative course. All but one (M.B.) had at least one episode of rejection prior to the diagnosis of lymphocoele.

In two patients (J.G. and L.R.) there was considerable limb swelling, so severe in one that he was treated with anticoagulants for a presumed iliac vein thrombosis before the diagnosis of a lymphocoele was made. Of the remainder, four had symptoms of lower abdominal discomfort. In five there was considerable hold-up of excretion of tracer from a dilated collecting system and pelvis. This is illustrated in Fig. 1A (N.B.) where the lymphocoele is seen as a relatively photon-deficient area lying at the lower end of the ureter. His IVU is shown in Fig. 1B. Post-operatively there was marked reduction in pelvic size with return to normal drainage, though the ureter remained slightly dilated (Fig. 1C).

One patient (J.G.), who was hypertensive, was found to have arterial stenosis by renal arteriography and at operation the renal vessels were found to be stretched tightly over the



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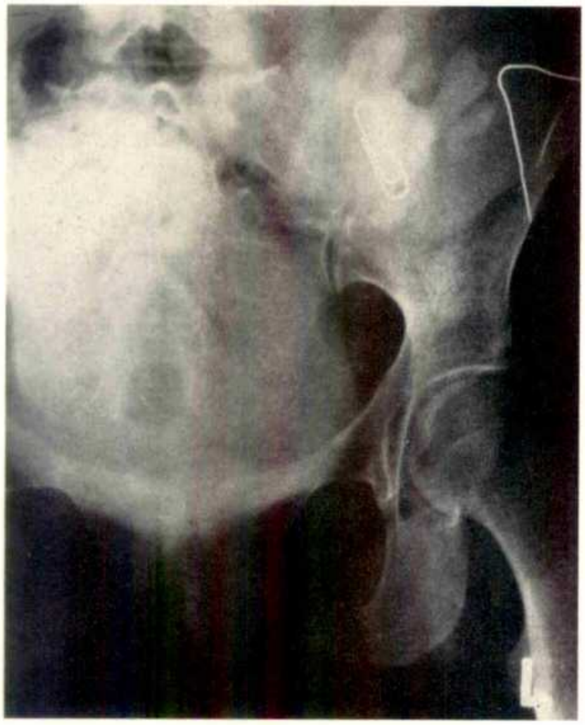
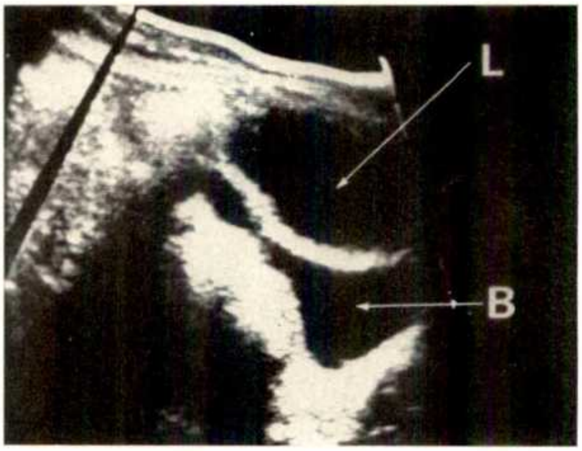


B

FIG. 2. (J. W.)

(A) Thirty-minute image showing the photon deficient lymphocoele lying between the kidney and bladder causing distortion of the bladder.

(B) IVU (the paper clips were for marking the kidney prior to radiotherapy) showing partial hold up of contrast excretion.



C

FIG. 2. (J.W.)

(C) Ultrasonography: Longitudinal sweep, 2 cm to the left of the midline. (L=lymphocoele. B=bladder. Head towards left.) This shows the transonic lymphocoele lying anterior to the bladder.

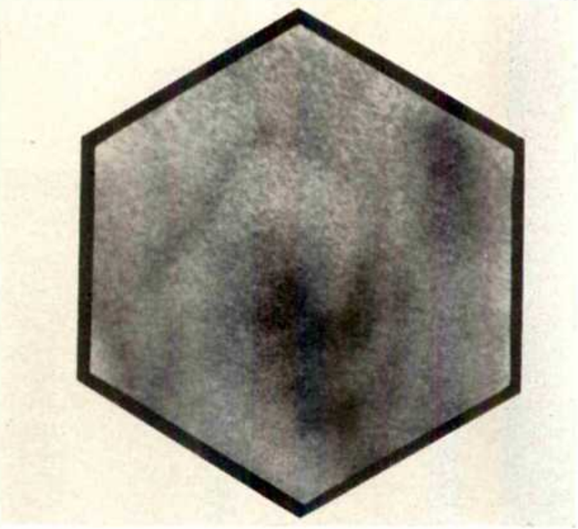


FIG. 3. (L.R.)

Thirty-minute image showing the photon deficient lymphocoele surrounding the renal image.

lymphocoele, but there was no ureteric obstruction. Following drainage of his lymphocoele, control of his hypertension became easier.

Three patients had their lymphocoeles confirmed by ultrasonography pre-operatively. The scintigram of one (J.W.) is shown in Fig. 2A. The lymphocoele is seen lying between the bladder and the kidney, with displacement of the bladder to the right. Her IVU is shown in Fig. 2B and the ultrasound examination in Fig. 2C, where the lymphocoele is seen as a transsonic area lying anterior to the bladder.

All the lymphocoeles were confirmed at operation. The volumes are only approximate as the sac of the lymphocoele

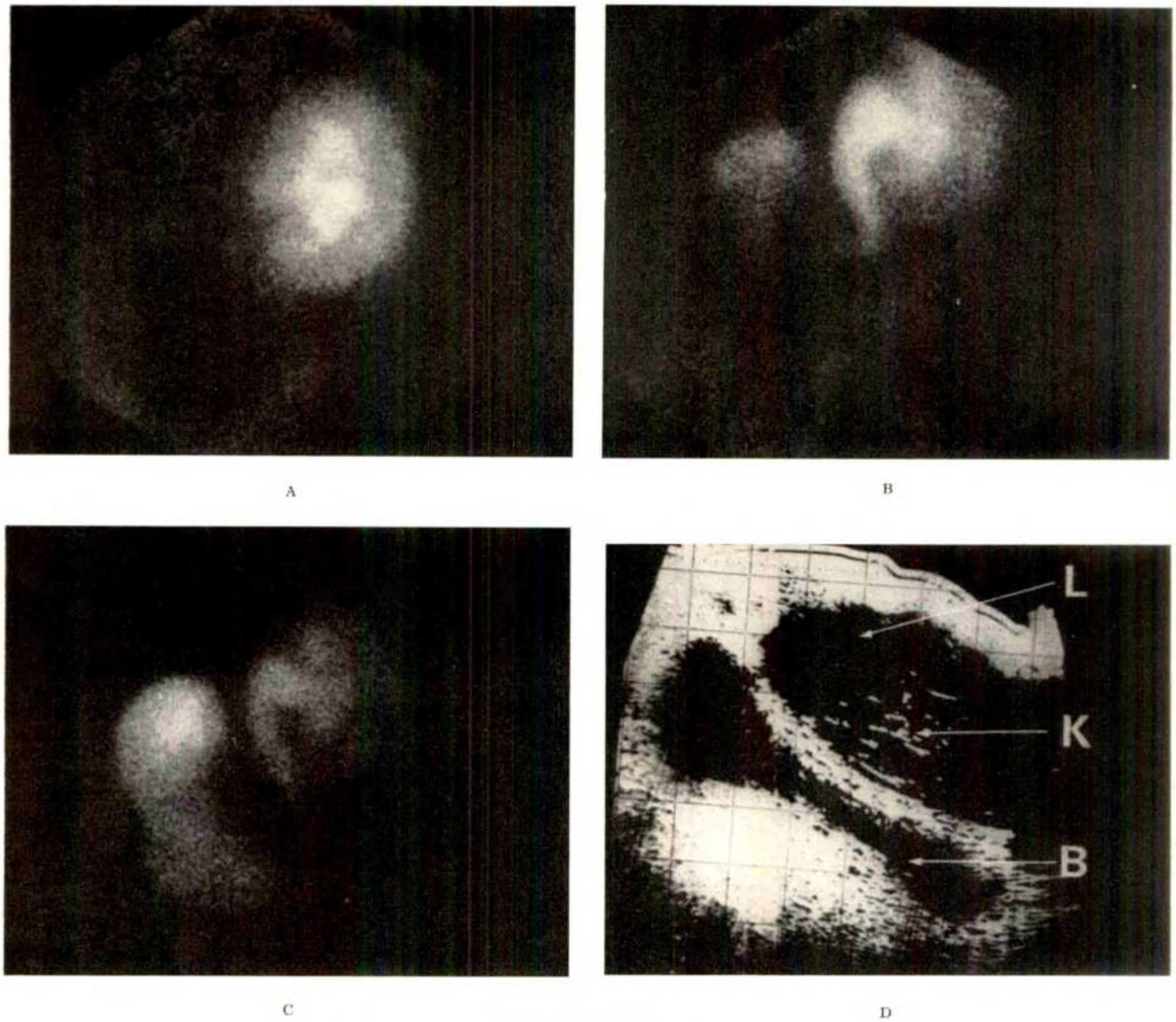


FIG. 4. (R.W.)

(A) Thirty-minute image showing the lymphocoele with the appearance of a normal full bladder.

(B) Post-micturition, showing tracer in the true bladder separate from the lymphocoele.

(C) Six-and-a-half-hour image, pre-micturition, showing greater distortion of the bladder by the lymphocoele.

(D) Ultrasonography: Mid-line, longitudinal sweep. (L=lymphocoele, K=kidney, B=bladder. Head towards left) Showing the lymphocoele as a transonic structure separate from the bladder.

was almost invariably punctured inadvertently. All were marsupialized and drained into the peritoneum and there has been no recurrence. The eighth patient (L.R.) who has since died, developed a second lymphocoele at a different site, one month after operation to drain the first. This was also drained subsequently.

DISCUSSION

There were three features we found to be of value in detecting lymphocoeles. Firstly, the presence of a spherical photon deficient area between the kidney and the bladder, with or without dilation of the ureter above. Secondly, a photon-deficient area completely surrounding the kidney as illustrated in Fig. 3 (L.R.). Thirdly, displacement and distortion of the bladder by the extrinsic pressure of the lymphocoele. This is shown in Fig. 4 where the pre-micturition image (Fig. 4A) shows a large photon deficient area which looks like bladder, but after micturition (Fig. 4B) the bladder is seen as a small, mushroom-shaped area above it. Six hours later, the bladder has filled more completely and the distortion is more apparent (Fig. 4C). The ultrasonographic appearances are shown in Fig. 4D.

Lymphocoeles are visible on scintiscans because of the comparatively slow exchange of fluid between the extracellular space and the contents of the lymphocoele, allowing the latter to become relatively photon deficient when compared to the background. The differential diagnosis on scintigram of a photon-deficient area includes urinoma, haematoma, full urinary bladder before the entry of tracer and a non-perfused kidney (Corcoran *et al.*, 1976).

Ultrasonography is probably the best investigation for confirmation of a lymphocoele (Nesbit *et al.*, 1976) because of the better intrinsic resolution of ultrasound, but it is very important to be aware of the appearances of lymphocoeles on scintiscanning so that they are recognized early when patients are being studied sequentially. It is worthy of note that in three cases the lymphocoele was not demonstrated in the pre-operative IVU, though in one of those it was clearly visible in a micturating cystogram.

ACKNOWLEDGMENTS

We gratefully acknowledge the permission of Mr. M. Bewick, Mr. F. G. Ellis, Professor J. S. Cameron, Dr. C. S. Ogg and Dr. D. G. Williams to report on their patients and thank Dr. B. C. King for the ultrasound studies.

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Book review

Quality Control in Nuclear Medicine. Ed. Buck A. Rhodes, pp. xvii + 508, illus., 1977 (C. V. Mosby Co., USA; distributed in U.K. by Henry Kimpton, London.) £31·60.

No service is reliable unless its quality is consistent. Nowhere is this more important than in medicine where clinical decisions may be influenced by, or even depend upon, the results of scientific investigations. The recipient of such data must be aware that scientific measurements are not absolute and are valid only within certain limitations. These limitations must be clearly stated and maintained and the process of ensuring such consistency is known as "quality control".

Few branches of the scientific service which aids medical diagnosis and the clinical management of patients have been more misunderstood, misinterpreted, and subjected to hasty policy decisions than has nuclear medicine. By its nature precise quality control was almost impossible in the early stages of its development but the situation has now greatly improved and continues to do so.

This book surveys the whole field of nuclear medicine from the point of view of quality control. Its editor has put a very wide definition upon this term so that the book is much more valuable and of wider scope than might be inferred from its title. The medical man or scientist responsible for other diagnostic services, radiological or laboratory, would glean sound wisdom from the less specialized parts of the book such as sections one (The Nuclear Diagnostic System) and two (Human Factors). These deal with matters applicable far outside the limits of nuclear medicine.

The sections on radiopharmaceuticals, nuclear instrumentation, and *in vitro* assays are, of necessity, of more appeal to specialists in these areas. Even where the matters under consideration are highly specialized, the clear and concise style which characterizes the book is retained.

A reader who has paid the high price for the book from his personal resources may well feel that the essentials could have been conveyed much more briefly and on less expensive paper in a less expensive binding, but if, like this reviewer, he can enjoy and profit from the book without paying for the privilege, the cartoons and diagrams, the clear and easy style, and the appendices, are all pleasurable. The practical value of the book is enhanced by the numerous references and adequate index.

E. S. Williams.

1978, *British Journal of Radiology*, *51*, 347–350 MAY 1978

Tuberculous erosion of the sphenoid bone

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(*Received August, 1977 and revised form December, 1977*)

ABSTRACT

Sphenoidal erosions due to tuberculosis are reported in four young coloured children. The lytic destruction is emphasized for reference texts indicate that tuberculosis produces a sclerotic reaction when extending to the skull base.

Tuberculous osteitis of the skull occurs particularly in coloured children and adolescents. It should be considered when destructive skull lesions are seen in these patients.

Tuberculous osteitis of the skull base is rare. Most standard radiological text-books do not mention the diagnosis, and reference works on skull radiology note only that tuberculosis may produce bony sclerosis when extending to the base (Du Boulay, 1965; Newton and Potts, 1971; Pendergrass *et al.*, 1956). This report concerns four children with tuberculous erosion of the sphenoid bone. Lytic destruction was the striking feature and sclerosis was totally absent in two of the cases. Two of the cases (cases 3 and 4) have previously been described in this Journal as examples of "multiple bone tuberculosis in the young" (Cremin *et al.*, 1970). This report therefore includes only details relevant to their skull radiology.

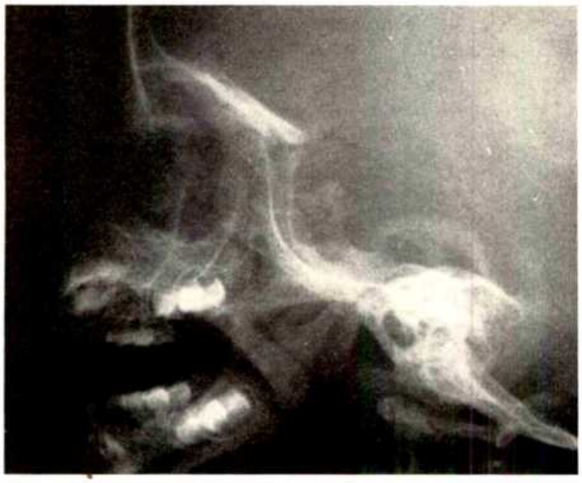

FIG. 1. *Case 1.*

Lateral view of skull. The planum sphenoidal and posterior part of the cribriform plate are destroyed.

CASE REPORTS

Case 1

A two-year-old coloured girl who weighed 10 kg, presented with anorexia, drowsiness and bilateral proptosis. Her optic discs were blurred and the Mantoux test was positive. The cerebrospinal fluid contained 240 mg % protein, 97 mg % chloride, 2.5 mg % glucose and each cubic

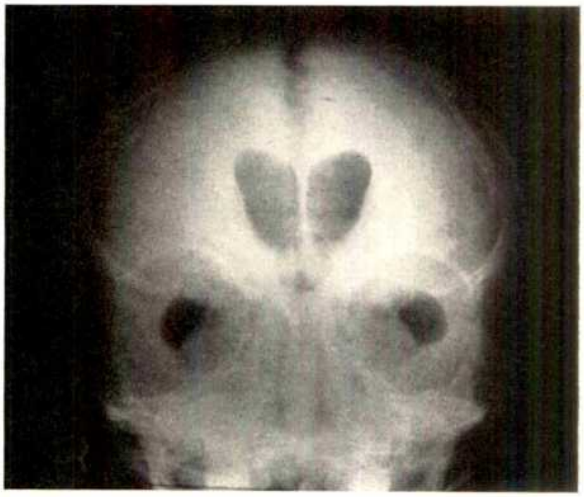

FIG. 2A. *Case 1.*

Air-encephalogram showing dilated ventricles and the absence of air over the cortex.

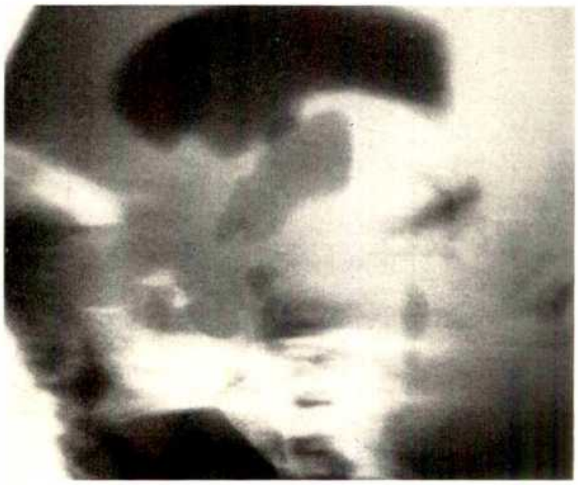

FIG. 2B. *Case 1.*

Mid-line lateral tomogram at air encephalography. The sphenoidal destruction and dilated ventricles are shown.

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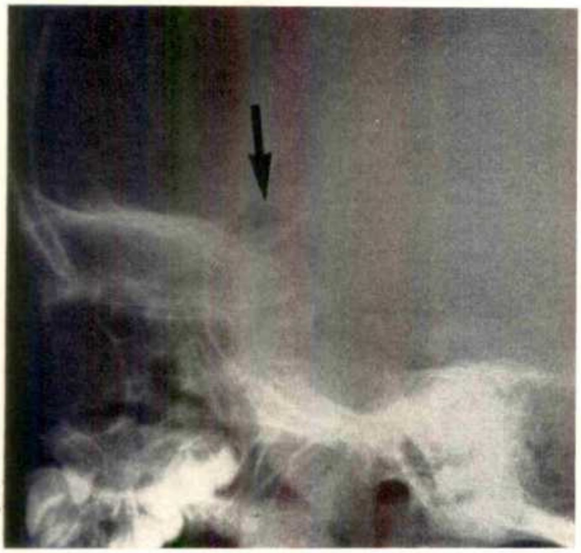

FIG. 3. *Case 2.*
Lateral skull view. A small lytic temporal lesion is arrowed. Porotic dorsum sellae.

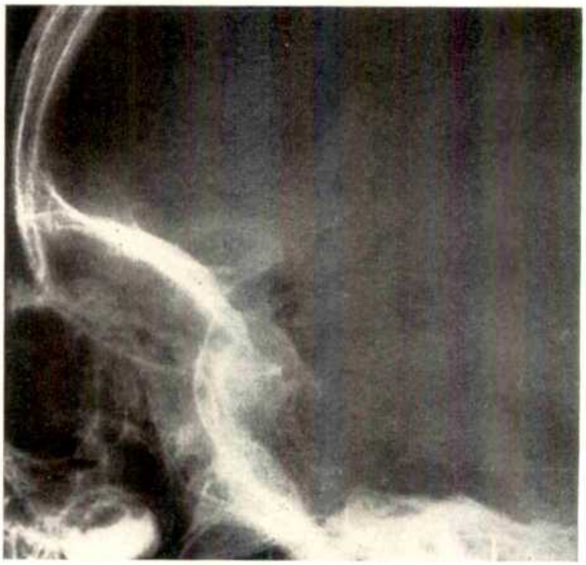

FIG. 4A. *Case 2.*
Lateral skull view taken post-operatively three weeks after Fig. 3. Marked destruction of the dorsum sellae and floor of the pituitary fossa.

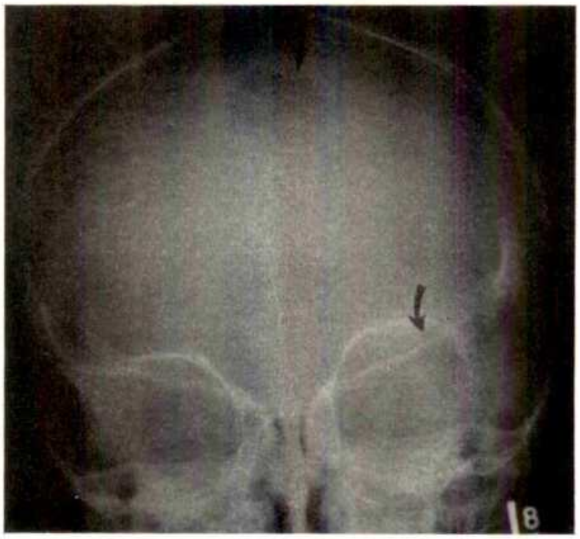

FIG. 4B. *Case 2.*
P.A. view. The operative defect adjacent to the zygomatic process of the frontal bone (curved arrow) and the large lytic defect high in the frontal region (straight arrow) are seen.

millimetre contained 124 polymorphs and 272 lymphocytes. No organisms were seen, but the bromide partition test ratio was 1.45.

The chest radiograph was normal, but destruction of the planum sphenoidale was seen on the skull radiograph (Fig. 1). An isotope scan and a carotid angiogram were undertaken, but were not contributory. Air encephalography showed moderately dilated lateral ventricles (Fig. 2A and 2B). No extension of the mass into the cranial cavity was seen and air did not pass over the cortex. Tuberculous meningitis with communicating hydrocephalus was diagnosed. A trans-ethmoidal sphenoidectomy showed granulation tissue over the cribriform area of the ethmoidal cells. The sphenoid body was eroded and caseous material was found in the sphenoid sinus. Histology of this showed tuberculous granulomata with large giant cells.

Case 2

A two-year-old coloured girl who weighed 9 kg, presented with a three-week history of strabismus and of a swelling posterior to the left lateral orbital margin. A left lateral rectus palsy was found, but no papilloedema or other positive findings were noted. The Mantoux test was positive, but urinary V.M.A. estimations were normal. A chest radiograph, hilar tomography and I.V.P. were also negative. A radiological skeletal survey showed a small lytic area adjacent to the scalp swelling in the left anterior temporal region and some osteoporosis of the dorsum sellae (Fig. 3). The swelling was explored surgically and the involved bone was removed without opening the dura. Histology of the removed material showed caseating tuberculosis and tubercle bacilli were identified on microscopy and culture. Medical treatment was started two weeks after presentation with Streptomycin 500 mg daily, P.A.S. 500 mg three times a day, and Isoniazid 40 mg three times a day. Repeat radiographs taken three weeks after the initial skull radiograph showed that gross destruction of the pituitary fossa was now present with a large lytic lesion in the high frontal region (Fig. 4A and 4B).

Case 3

A two-year-old African boy who weighed 11 kg presented with a two month history of painless swelling of the right ring finger and an ulcer over the dorsum of the foot. Examination showed generalized lymphadenopathy with hepatosplenomegaly, and symptomless proptosis of the left orbit. The Heaf test was positive and a gland biopsy showed caseating tuberculous lymphadenopathy. A chest radiograph was negative, but a skull radiograph showed erosion of the sphenoidal wings on the left side, with destruction of the posterior wall of the left orbit (Fig. 5). The radiographs of

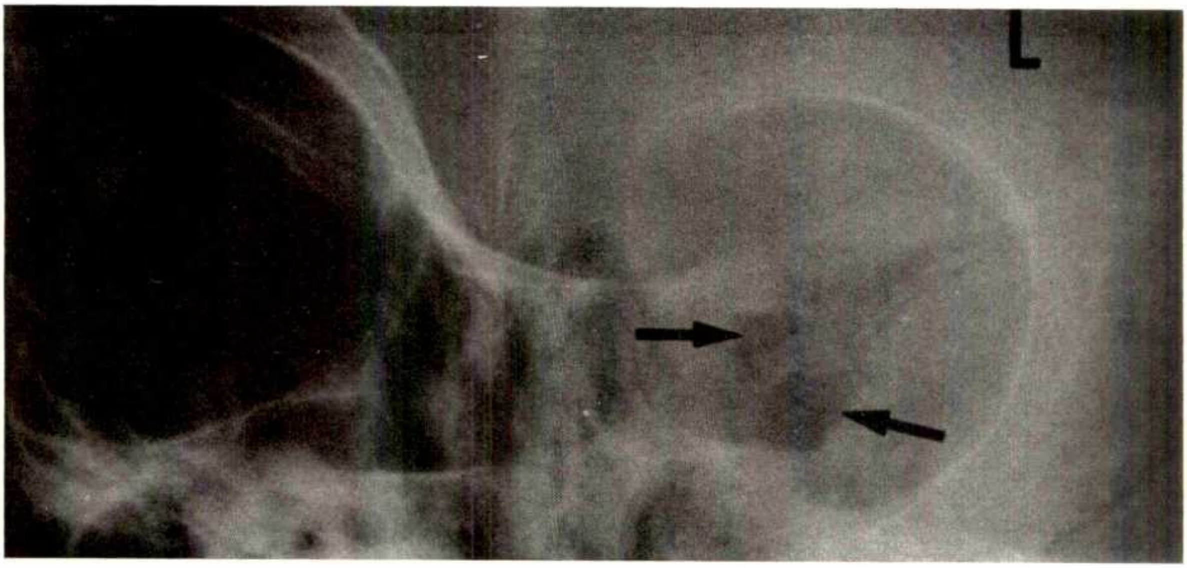

FIG. 5. *Case 3.*
Oblique view. Destruction of the posterior wall of the left orbit is seen with lytic defects in the sphenoidal wings above and lateral to the irregular optic canal and superior orbital fissure (arrowed).

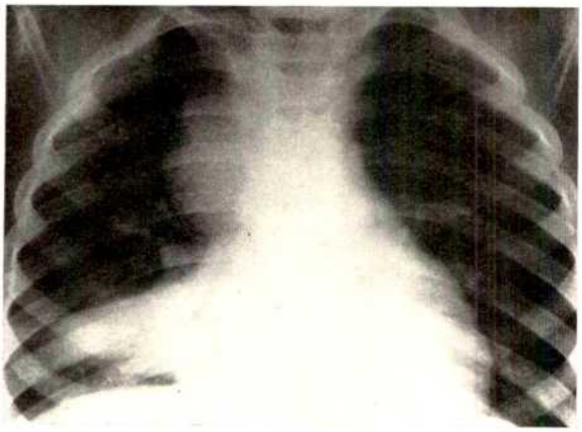

FIG. 6. *Case 4.*
Mediastinal lymphadenopathy with middle and right lower lobe consolidation.

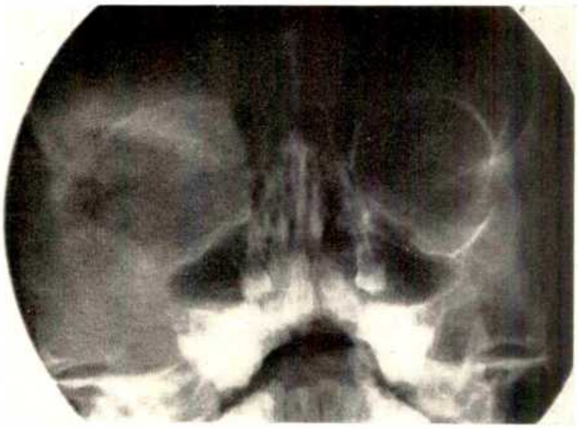

FIG. 7. *Case 4.*
Extensive sclerotic lesion of the right orbit and zygoma with lytic destruction of the right sphenoidal wings.

the limbs showed cystic multilocular lesions in two phalanges, a metatarsal and the left ulna.

Case 4

A six-year-old African boy who weighed 15 kg presented with a six-month history of swelling of the right orbit. An abscess was present over the sternum and the Heaf test was positive. The chest radiograph showed right middle and lower lobe consolidation with enlarged mediastinal glands (Fig. 6). The skull radiograph showed marked sclerosis of the bony margins of the right orbit, but extensive lytic destruction of the posterior wall of the right orbit and greater wing of the sphenoid (Fig. 7).

DISCUSSION

Skull involvement has been reported in 0.1 to 3.7% of cases of tuberculous osteitis (Ganguli, 1963; Strauss, 1933). Skull disease is more common in pigmented races (Jacobs, 1964) and more prevelent in childhood, half the cases presenting before the tenth year (Strauss, 1933). The typical lesion is an irregular, lytic erosion of the calvarium.

Basal involvement is rare and we have only been able to trace descriptions or illustrations of four other cases in the literature (Pendergrass *et al.*, 1956; Miles and Hughes, 1970). Pendergrass stated that tuberculosis seems to produce a different type of bony change when extending to the skull base, usually a much increased density of the bone. He illustrated this statement with two cases showing marked sclerosis around the pituitary fossa, but did not give full clinical details of the patients. Other neuro-radiological text-books either quote these cases (Newton and Potts, 1971) or say that tuberculosis may produce a sclerotic reaction when extending to the base (Du Boulay, 1965). However, sclerosis should not be regarded as the hallmark of basal tuberculosis, for two cases presenting in the English midlands to Miles and Hughes (1970) and two of our cases showed entirely lytic destruction. Our other two cases showed no more than minimal sclerosis in the sphenoid bone.

Cranial tuberculosis is usually associated with tuberculosis elsewhere in the body (Strauss, 1933). In our first two cases cranial disease was the only manifestation, and our first three cases had normal chest radiographs. It is clear that tuberculous osteitis must not be excluded on the basis of a normal chest radiograph. The association of sphenoidal destruction with tuberculous meningitis in our first case is also of interest, for tuberculous meningitis was seen in only ten of 223 cases of skull tuberculosis reported by Strauss (1933).

Our four patients were all underweight coloured children. Jacobs (1964) reported 30 cases of tuberculous osteitis from Birmingham emphasizing the differences of bony tuberculosis in coloured races, while Walker (1968) reported 18 new cases of tuberculous osteitis from Stanmore, noting that half of these had been mis-diagnosed initially. It is clear that tuberculous osteitis is still a problem in British hospitals. The unusual forms of the disease which are particularly seen in non-white races may often be overlooked. Tuberculosis should be considered when irregular lytic destruction of the sphenoid bone is seen in young, coloured patients.

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Book review

Manuel de techniques radiographiques du crane. By G. Korach and J. Vignaud, pp. 144, illus., 1977 (Editor Masson, Paris, New York, Barcelona, Milan), 120F.

This book written for radiographers is a model of what a monograph should be. It is short yet comprehensive. The brief text written in simple French is subdivided by multiple headings and is supplemented by excellent photographs, radiographs and line drawings which are virtually self-explanatory. The dead wood has been cut away. Projections valuable in their time but now replaced and non-essential variants of projections are dismissed. Stress is laid on definition of projection by the axis of the central ray and the anatomical structure being radiographed.

The book is divided into three parts. The first deals with general principles including image quality, tomography, magnification and definition of projections. The second describes and illustrates the projections and the resulting radiographs. The third consists of pertinent tables which are useful for reference to the projections appropriate, for example, to the various foramina and includes notes on the symptoms produced by lesions of the structures related to them. There is a selected bibliography and an adequate index.

A really refreshing and important aspect of this book is the stress placed on the radiographer understanding the reason for the examination, the anatomical structures involved in producing the symptoms and the radiographic principles of demonstrating the relevant region to the best advantage. It cannot be too highly recommended.

B. KENDALL.

1978, *British Journal of Radiology*, *51*, 351–356 MAY 1978

Perinatal post-mortem radiography—experience with 2500 cases

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ABSTRACT

A review of 2500 routine post-mortem radiographic examinations of perinates is presented. It is concluded that the procedure is of value in the detection of abnormalities which may have contributed to the death of the perinate and which may have escaped detection at autopsy. The use of contrast agents may assist in the evaluation of congenital abnormalities, especially of the cardiovascular system. Post-mortem radiographic examination may be especially helpful in the evaluation of perinates for whom permission for autopsy is denied. Post-mortem radiography may assist in the gathering of statistical data and may provide useful material for teaching and research.

Routine post-mortem radiography of stillborn babies and neonates was introduced into the National Women's Hospital in 1964, as an aid to the evaluation of the cause of death. Since that time, over 2500 examinations have been performed. Additional information was obtained in some cases by post-mortem contrast examination and in other cases by radiography of specimens excised at autopsy. A review of these cases forms the basis of this communication.

I. ROUTINE POST-MORTEM RADIOGRAPHY

Technique

Whole body A.P. and lateral radiographs are obtained on all stillbirths and neonates dying in the National Women's Hospital. Additional views of areas of interest may be obtained.

Kodak RPR film with fine grain screens is used with a Potter-Bucky diaphragm. Occasionally mammography film is used, when additional detail is required; for example, for fine bone detail or when pathological calcification is suspected on the standard films. In our opinion the detail provided on standard film is adequate in most cases.

The dead infants are brought from the mortuary to the radiology department in the morning before the autopsy session. The films and the radiologist's report are delivered to the pathologist before the autopsy, so that the examination can be planned accordingly.

Results and discussion

Significant findings on routine post-mortem radiographs included abnormal collections of intra-thoracic and intra-abdominal air, cranio-spinal abnormalities, skeletal abnormalities including bone dysplasias, and pathological calcification. Of the 2500 examinations reviewed, 454 (18.2%) showed at least one such abnormality.

Evidence of abnormal collections of intrathoracic air was found in 87 cases. There were 26 cases of pneumoperitoneum. As detection of such air collections at autopsy is unreliable, radiography provides the only accurate means of doing this. Pneumothorax or pneumopericardium may be a major contributing factor in the death of an infant receiving positive pressure ventilation. Such a case is demonstrated in Fig. 1; a large pneumopericardium was an unsuspected finding on post-mortem radiographs of an infant who suffered from the idiopathic respiratory distress syndrome and was being managed with assisted ventilation.

Air embolism may be a cause of sudden death, especially in babies with the idiopathic respiratory distress syndrome (Gregory and Tooley, 1970; Vinstein *et al.*, 1972; Shook *et al.*, 1975). This diagnosis may be suggested by the identification of air within the heart or systemic circulation. Quisling *et al.*, (1974) have demonstrated that intravascular gas may accumulate rapidly as a post-mortem phenomenon, implying that unless radiographs are obtained immediately after death, the diagnosis of air embolism cannot be made with confidence. Our experience suggests, however, that this is an unusual occurrence as intravascular gas was visualized in only a few radiographs of neonates obtained several hours after death. Indeed, we have observed instances where there has been a reduction in the amount of gas after death and this is supported by other authors (Van Allen *et al.*, 1929; Shook *et al.*, 1975). In either event, however, the necessity is established for obtaining radiographs as soon as

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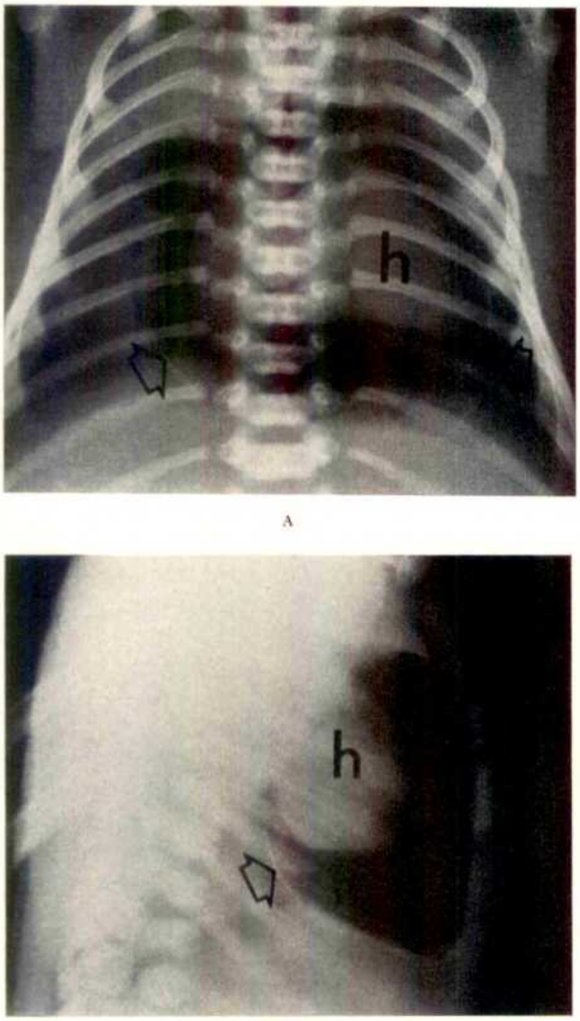
Presented at International Congress of Radiology, Rio de Janeiro, October 1977.



A

B

FIG. 1.

(A and B): Pneumopericardium and pneumomediastinum. A.P. and lateral views of the chest, cropped from whole body post-mortem radiographs. This baby died at 32 hours, after management with positive pressure ventilation for idiopathic respiratory distress syndrome. Chest radiographs eight hours before death had shown bilateral pneumothoraces, treated with intercostal drainage tubes. Post-mortem films revealed a massive pneumopericardium with compression of the heart (h). The pericardium is outlined by air in the pericardial sac and the mediastinum (arrows).

possible after death, especially following the sudden deterioration and death of an infant receiving positive pressure ventilation. Poznanski (1976) recommends that the examination should preferably be performed while the dead infant is still in the nursery and before any umbilical arterial or venous catheters have been disconnected, since air could enter the vascular tree in this manner.

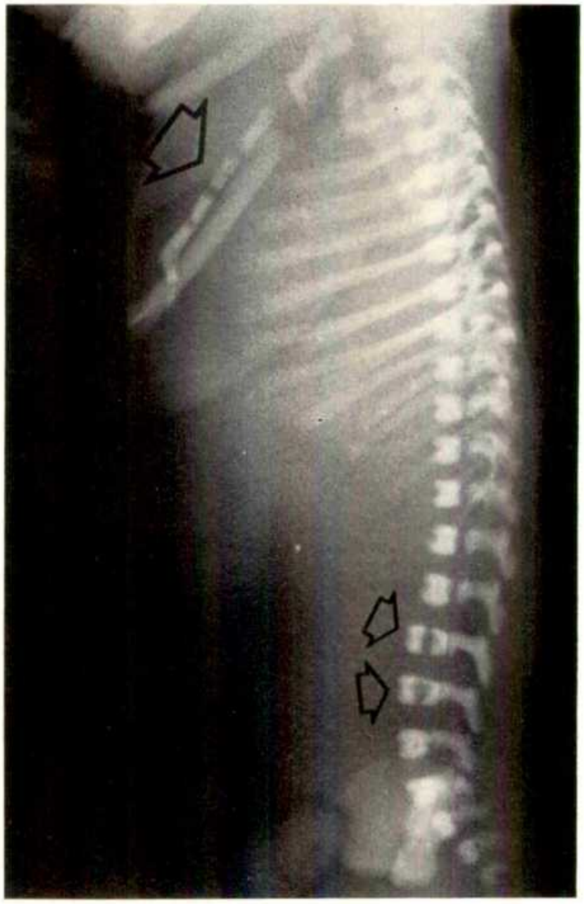


FIG. 2.

Minor skeletal anomalies disclosed by post-mortem radiography. Anomalous ossification of the sternum (large arrow) and coronal cleft vertebrae (small arrows) in a neonate who died of congenital heart disease.

Abnormalities of the skeleton may escape detection without post-mortem radiography, especially if they are localized and relatively minor (Fig. 2). Post-mortem radiography may assist in the evaluation of severe cranial and skeletal deformities. The commonest abnormal condition demonstrated in this series was anencephaly, 122 cases being documented. This represents an approximate incidence of one anencephalic in 1190 births. Previous estimates of the incidence of anencephaly range from one in 8300 births in Lyons, to one in 150 births in Belfast (Penrose, 1957).

Ryan and Kozlowski (1971) pointed out that without post-mortem radiography the diagnosis of lethal bone dysplasias is not possible. As a result, the frequency of the dysplasias cannot be known and the genetic implications of an abnormal baby cannot be

TABLE I

ANALYSIS OF 25 CASES OF BONE DYSPLASIA

Osteogenesis imperfecta, Recessive	8
Osteogenesis imperfecta, Dominant	2
Chondrodysplasia punctata, Recessive	5
Chondrodysplasia punctata, Dominant	1
Thanatophoric dwarfism	4
Short rib—Polydactyly syndrome (Majewski type)	2
Achondroplasia	1
Achondrogenesis, Type II	1
Spondyloepiphyseal dysplasia congenita	1

accurately considered. In our series there were 25 babies shown to have bone dysplasias (Table I). It is possible, from these figures, to calculate the incidence of those dysplasias which are incompatible with life and would therefore have all been included in this study. In those dysplasias where survival is possible, the figures obtained from this survey can be added to those obtained from other sources and the approximate incidence calculated. The incidence of bone dysplasias in our population is being evaluated in this way and will be presented in a future communication.

Demonstration of centres of ossification on post-mortem radiographs may assist in the assessment of maturation of the stillbirth or dead neonate, which is important for statistical purposes and may assist in the evaluation of the factors leading to the death of an individual case. It has been established, however, that ossification is quite variable and provides only a rough estimate of the gestational age (Farr, 1968; Kuhns and Finnström, 1976). Assessment of osseous maturation may be of value, however, in detecting disease states or syndromes in which ossification is retarded, advanced or altered in sequence. The criteria for this assessment and tabulation of the associated conditions have recently been presented by Kuhns and Finnström (1976).

II. POST-MORTEM CONTRAST RADIOGRAPHY

Technique

The cardiovascular system may be examined in the dead infant by the introduction of radio-opaque contrast agents through in-dwelling umbilical vascular catheters, or through catheters introduced into the umbilical vessels or other major arterial or venous trunks after death. Contrast medium can also be utilized to display other organ systems—for example, bronchography is easily performed by introducing contrast media through an endotracheal tube. Vascular catheters can be manipulated under fluoroscopic control into the optimum position for injection in each case. The injection is made by hand and the appropriate spot films obtained. It is sometimes necessary to turn the infant and utilize the effect of gravity to obtain maximum vascular filling.

Any water-soluble contrast agent or thin barium suspension is suitable for this examination. The contrast medium usually mixes evenly with the blood and post-mortem clot formation does not present a problem. Exquisite detail of fine vessels may be obtained (Fig. 3).

Overlapping of opacified structures is a problem that may be encountered. Attempts to aspirate contrast medium after injection are generally unsuccessful. It is therefore necessary to plan the sequence of contrast medium injections to obtain maximum information. For example, in a neonate suspected on radiographs during life to have bilateral aplasia of the upper lobes, (Fig. 4), the first injection made was into the bronchial tree. The injection was stopped once the characteristic blind-ended bronchi of lobar aplasia had been identified and the bronchial tree to the lower lobes was shown to be grossly normal. As a result, the subsequent demonstration of an anomalous arterial supply to the right lower lobe from the abdominal aorta was not obscured.

Discussion

Post-mortem angiocardiography has been recommended as a useful diagnostic method in congenital heart disease (Richter, 1976). Topographical relationships, especially of the cardiac chambers and great vessels, will be disturbed at autopsy and often difficult to evaluate. Post-mortem angiocardiography, on the other hand, will generally demonstrate the topography very clearly. Different heart chambers and vessels can be simultaneously filled with contrast medium and radiographs obtained in various projections. Similarly, pathological details may be demonstrated which were obscure on angiocardiograms performed during life.

The limitations of post-mortem angiocardiography have been pointed out by Richter (1976). In particular, functional problems cannot be evaluated, such as the direction of blood flow. Chamber size and vessel diameter may vary with the extent of contraction of the muscle, with the pressure used for injection and with the amount and type of contrast medium. In spite of these limitations he concludes that post-mortem angiocardiography may be a help in diagnosing complicated congenital malformations of the cardiovascular system. Our experience supports this conclusion.

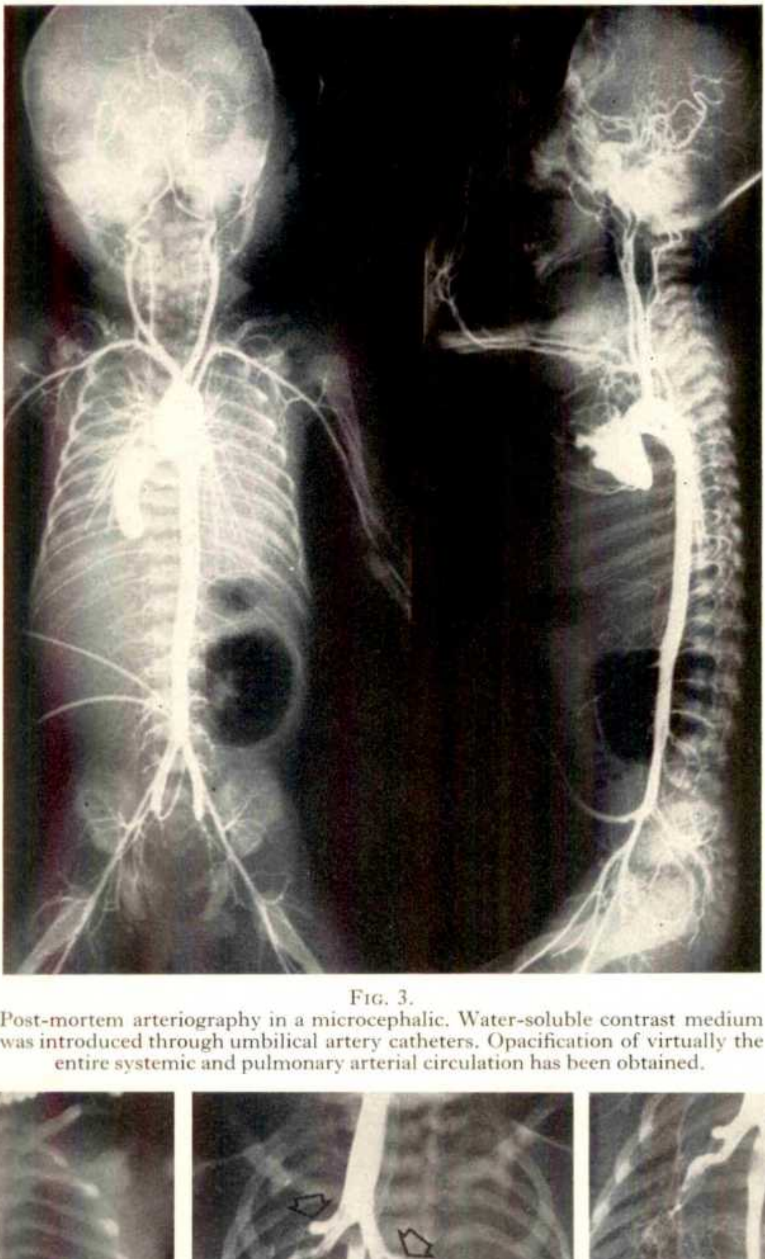
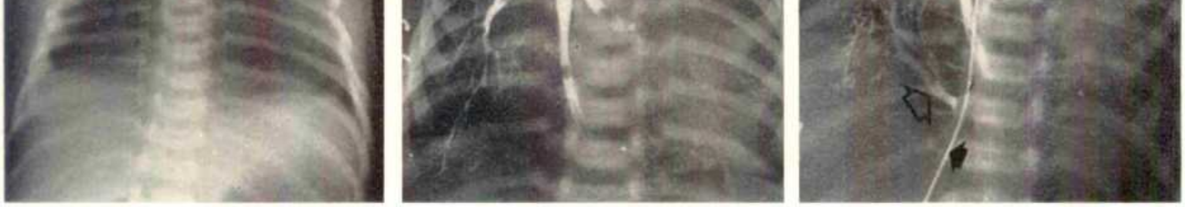


Fig. 3.
Post-mortem arteriography in a microcephalic. Water-soluble contrast medium was introduced through umbilical artery catheters. Opacification of virtually the entire systemic and pulmonary arterial circulation has been obtained.



A B C

Fig. 4.
Congenital venolobar syndrome.
(A) A.P. chest film at 4 hours of age. The heart outline is obscured by a bilateral veiling density. (B) Post-mortem bronchography reveals the characteristic blind-ended bronchi of aplasia of the upper lobes (arrows). The esophagus also contains contrast medium. (C) Contrast medium introduced through an umbilical artery catheter in the aorta (arrow) opacifies the arterial supply to the right lower lobe, arising from the coeliac axis artery (open arrow).

Post-mortem radiography is of special value in those cases in which permission to perform an autopsy is not obtained. In many instances it is possible to supplement the routine radiographs with contrast studies. In the case illustrated in Fig. 4 we wished to confirm our ante-mortem diagnosis of bilateral aplasia of the upper lobes, especially as we were unable to find any previously reported cases of bilateral aplasia in the literature. As permission for autopsy was not granted, we introduced contrast medium through the endotracheal tube and through an umbilical artery catheter before these were removed after death. This confirmed the diagnosis of bilateral aplasia of the upper lobes and displayed an anomalous arterial supply to the right lower lobe. Because of ethical considerations we do not perform cutdown operations on vessels in those babies for whom permission for autopsy is refused. If indwelling catheters are not present in these cases it is sometimes possible to catheterize the umbilical vessels directly.

III. POST-MORTEM SPECIMEN RADIOGRAPHY

Radiography of tissues that have been excised at autopsy may assist in the evaluation of abnormalities disclosed either during the course of the post-mortem examination or on the pre-autopsy radiographs. Such radiographs are often of special value as teaching material. For example, fine bone detail can be obtained on mammography or industrial film. The distribution of intracerebral calcification in congenital toxoplasmosis can be clearly demonstrated by obtaining radiographs of the excised brain. Contrast agents may be utilized in the demonstration and evaluation of abnormalities discovered by autopsy. For example, a section of bowel may be radiographed to demonstrate a stricture or other abnormality found at autopsy. This is done by closing the bowel lumen at each end with clamps and injecting air or water-soluble contrast medium. Figure 5 illustrates a case in which injection of contrast medium into the thoracic duct at autopsy showed it to be dilated and tortuous and apparently obstructed at its opening into the venous system. This stillborn infant was markedly oedematous with a massive right pleural effusion and marked hypoplasia of the right lung.

Techniques for inflating and radiographing excised neonatal lungs have been described (Robertson and Söderlund, 1972; Lallemand and Van Duc, 1973). Information gained in this way has led to a better understanding of pulmonary anatomy and pathology in neonates, and may provide useful material for teaching and research.

CONCLUSIONS

A review of 2500 post-mortem radiographic examinations suggests that:

(1) Post-mortem radiography is of value in the detection of conditions which may have contributed to the death of the infant, especially pneumothorax, pneumopericardium and pneumoperitoneum. Air embolism may be diagnosed providing that the radiographs are obtained soon after death.

(2) The pathologist's attention may be directed to abnormalities such as pathological calcification and localized bone lesions, which might otherwise have been undetected at autopsy.

(3) Assessment of osseous maturation may be of value in the detection of disease states or syndromes in which ossification is retarded, advanced or dysharmonious.

(4) The procedure may assist in the gathering of statistical data. The frequency of lethal bone dysplasias can only be determined in this way.

(5) The use of contrast agents can assist in the delineation of pathological states, especially in the

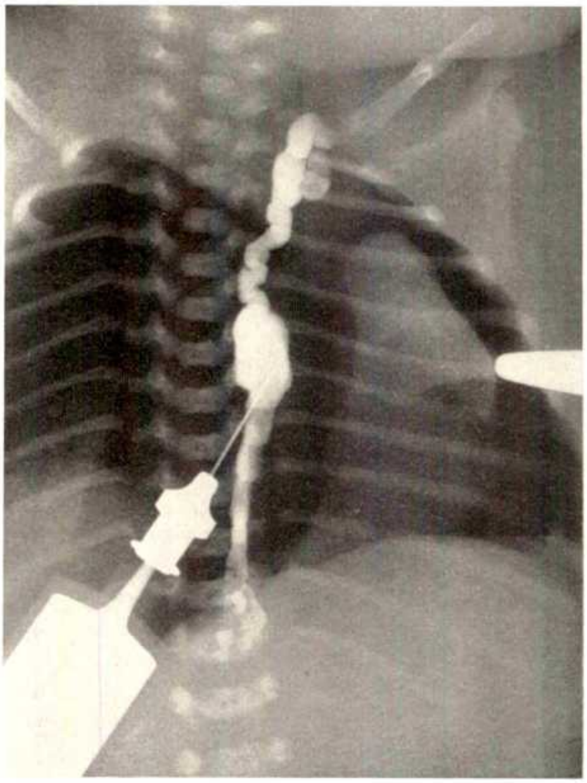


FIG. 5.

Dilated, tortuous and obstructed thoracic duct demonstrated by the injection of contrast medium at autopsy.

evaluation of complicated congenital cardiovascular anomalies.

(6) Radiography of organs or tissues that have been excised at autopsy may provide additional information to that obtained from pre-autopsy radiographs.

(7) Post-mortem radiography is of special value if permission to perform an autopsy is not granted. In such cases it may be possible to gain additional information by injection of contrast medium into indwelling catheters and tubes.

(8) Post-mortem radiographs are useful for teaching purposes and are a very useful adjunct to clinicopathological discussions.

Acknowledgments

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Book review

Pediatric radiology. Case studies. By Howard A. Wexler and Catherine A. Poole, pp. 377 illus., 1977 (Henry Kimpton Publishers, 7 Leighton Place, Leighton Road, London), £11·25.

This book consists of 81 case presentations illustrative of a wide variety of the problems which may present in the course of paediatric radiological practice. Such a method of presentation has many advantages, not the least of which is that the problems discussed and the solutions offered are related to the practical situations in which they occur in the course of daily work.

The approach is dogmatic, but there is a good discussion of the evidence upon which the conclusions are based with a comprehensive and up-to-date series of references to the relevant literature. The aim of the authors has been to pass on the fruits of their experience derived from their work in the Section of Pediatric Radiology in the University of Miami and in this they have been successful. There will be very few even of the "experts" in the field who will not learn something from reading this book and the multiple choice question type of format, while it may irritate some readers, will be of advantage to trainees preparing for examinations.

It is unfortunate, therefore, that the quality of the illustrations does not in general match up to that of the written part of the book and it is too frequently the case that the reader is unable to discover from the radiograph provided, the evidence that will enable him to reach the conclusions which it is designed that he should. At £11·25 this book is not particularly cheap and while it is obviously desirable in a book such as this to keep the cost as low as possible, this object should not be attained at the expense of adequate photographic reproduction. I. R. S. Gordon.

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Two regimes with the same TDF but differing morbidity used in the treatment of stage III carcinoma of the cervix

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ABSTRACT

As an alternative to five daily fractions per week, one large fraction per week has been used to treat patients with stage III carcinoma of the cervix. This regime was greatly appreciated by our village women who could attend for weekly treatment from their homes. The weekly dose was matched with our previously acceptable daily fractionation using NSD, TDF and CRE values. In 24 patients the early reactions and tumour response were acceptable. Late rectal complications commencing seven months after treatment have, however, developed in all surviving patients with the new regime. The complications have been far more severe than those of a matched group of 24 patients treated with daily fractions and the schedule using one fraction per week has been abandoned. "Iso-effective" doses for the two techniques were selected from the NSD, TDF and CRE tables. This study clearly indicates that for one fraction per week the doses predicted are not "iso-effective" as far as the normal tissues of the pelvis are concerned.

The tolerance of the normal tissues in and around a tumour is the restraining factor which limits the dose of radiation which can be delivered. An additional important cause of failure in radiotherapy is the significant number of hypoxic and viable tumour cells in most macroscopic tumours. The dose of X or γ rays required to sterilize these hypoxic cells is well above the normal tissue tolerance. Use of high LET radiation such as fast neutrons with a low oxygen enhancement ratio is one possible solution. On the basis of experimental studies several workers are of the opinion that X rays can be made as effective as fast neutrons by an otimum fractionated dose and interval between fractions (Fowler *et al.*, 1972). On the basis of experimental studies with C_3H mouse mammary carcinoma, Howes (1969) concluded that several large doses of X rays given at 48 hour intervals would almost eliminate the problem of hypoxic cells in the tumour and would therefore be as effective as treatment with neutrons. Since this different fractionation strategy utilizes physiological changes in the tumour to produce sensitization of target tissue, Elkind (1970, 1973) described it as physiological sensitization.

Intestinal mucosa has a very rapid cell turnover and Wiernik and Plant (1970) noted histological changes due to radiation damage after 24 hours. Newton (1964) and Edwards (1965) found gut to be also the most radiosentitive tissue for late radiation damage. In the radiotherapy of cervical carcinoma, bowel mucosa is the most radiosensitive tissue in the field of treatment. With megavoltage teletherapy and intracavitary radiation, the acceptability of a regime is determined by the acute as well as late radiation reactions developing in the bowel. The acute reactions are probably determined by the repopulation kinetics of the mucosal epithelium. The late reactions are, however, dependent upon damage to the vascular and connective tissue of the bowel wall (Rubin and Casarett, 1968). Epithelial repopulation following irradiation is related to the time-dose effect of radiotherapy and so the acute reactions can easily be kept within acceptable limits. It is on account of this that very high doses can be given by prolonging the duration of radiotherapy. This became popular a few decades ago but was soon abandoned on account of late radiation damage (Wiernik, 1973). The various iso-effect doses determined on the basis of the NSD formula (Ellis, 1967, 1969), TDF tables (Orton and Ellis, 1973) and CRE formula (Kirk *et al.*, 1971) are expected to produce a similar epithelial response. There is, however, little experimental or clinical information to prove or disprove that the iso-effect doses based on the above also hold true for the late reactions.

Wiernik (1973) quotes Freund (1927) that daily fractions had become the accepted standard from 1897 onwards and the latter was the first to report using gaps of 48 and 72 hours between fractions. A number of workers (Sambrook *et al.*, 1950; Sikov *et al.*, 1963; Atkins, 1964a, b) reported better tumour control by treating with one, two or three weekly fractions. All of them, however, reported unacceptable normal tissue damage with once weekly treatment regimes. The principles of relative biological effectiveness utilizing NSD, CRE, etc., were not applied by them in selecting the dose levels to be employed in the altered regimes of radiation treatment.

Even if the proportion of hypoxic cells in a tumour is as low as 10^{-3}, the ultimate control of the tumour is dependent upon the fate of these cells. One of the main aims of fractionation is to create conditions under which the hypoxic cells become oxygenated during the course of treatment. This requires that enough time should be available between fractions to allow for lysis of the dead cells. Disappearance of dead cells would reduce the distance between the capillaries and the surviving cells thereby making them better oxygenated and more vulnerable to the subsequent fractions. Many of the cells only die on attempted mitosis. According to Elkind (1973) it takes about three to four cell cycle times for oxic Chinese hamster cells to die and for lysis to take place and the same applies to rodent tumours. Elkind believes that if rates of cell degeneration in human tumours are also related to rates of cell growth, then fractionation intervals considerably in excess of 24 hours will be required to achieve effective reoxygenation. Repopulation during longer fractionation intervals may not be of much importance because human cells grow more slowly.

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With this background it was considered reasonable to test the efficacy of a course of treatment using one fraction weekly over a period of several weeks for stage IIIB carcinoma of the cervix. It was considered that even if this treatment proved to be only of equal effectiveness to the daily fractionation regime it would be far more acceptable to our patients. Most of our patients come from villages, accompanied by a number of family members. They find it difficult to stay in and around the hospital for six to eight weeks away from their place of work. One of the main reasons why patients come to us with such advanced disease is because the family likes to postpone the journey to the hospital until they can be away from their farms for this length of time. Weekly visits to the hospital do not disrupt their work. This weekly fractionation regime was immediately appreciated by them.

Material and Methods

Twenty-four consecutive patients with stage IIIB carcinoma of the cervix were treated by the weekly fractionation regime. Their response to treatment including tumour regression and early and late reactions were compared retrospectively with twenty-four consecutive patients treated by a daily fractionation regime during the same month in the previous year. A minimum period of follow up in all cases has been one year. Cobalt 60 teletherapy and intracavitary radium or caesium were used in all cases as detailed below:

Group I, daily fractionation

Depending upon the separation of the anterior and posterior pelvic fields, a dose of 3000–4000 rad was given in 20 daily fractions by a diamond-shaped field of size 15 × 15 cm, with an Eldorado A cobalt 60 teletherapy unit working at 80 cm SSD. Patients with a separation above 18 cm were given 3000 rad (midplane) and thinner patients were given a midplane dose of 4000 rad prior to intracavitary treatment. As soon as any diarrhoea settled, this was followed by an intracavitary insertion with an Ernst applicator (1949) giving a dose of 4000 rad to point A. A few days later further cobalt 60 teletherapy delivering approximately 1000 rad in five daily fractions was instituted. A total dose of 8000 rad was given to point A and 6000 rad to the pelvic wall. The central high dose area was shielded after the whole pelvis had received 4000 rad by cobalt 60 teletherapy.

Group II, weekly fractionation

The TDF tables of Orton and Ellis (1973) were used to determine the weekly dose. 4000 rad in 20 daily fractions at five fractions per week corresponds to a TDF of 66. With one fraction per week the same TDF was possible with five fractions of 580 rad each, given over 28 days, before the intracavitary radium insertion. Following the same dose of 4000 rad to point A with intracavitary radium or caesium with an Ernst applicator, another fraction of 670 rad was given to the pelvic wall. In some patients who had suffered from severe diarrhoea, this dose was kept at 580 rad. The dose of 670 rad was considered roughly equal to 1000 rad in five daily fractions. Six fractions of 580 rad are also only slightly less effective biologically than 25 fractions of 200 rad according to the TDF tables.

The rectal dose was calculated according to dose distribution charts (Ernst, 1958). A rectal dose-rate meter manufactured by Bhabha Atomic Research Centre, Bombay, was also used. The two calculations had a variation of only 5–10%. The higher reading was used for calculation of rectal dose from the intracavitary insertion. In both groups the radium dose to the rectum varied from 2050 rad to 2580 rad. In group I the total rectal dose thus varied from 6050 to 6580 rad. If we take 2900 rad given in five once-weekly fractions to be biologically equivalent to 4000 rad then the rectum received a similar dose in both groups of patients. In several patients of both groups the last five fractions in group I and last fraction in group II of external irradiation were postponed by one to three weeks because of side effects. These parametrial fractions, however, did not contribute a significant dose to the rectosigmoid. The total duration of treatment was similar in both groups.

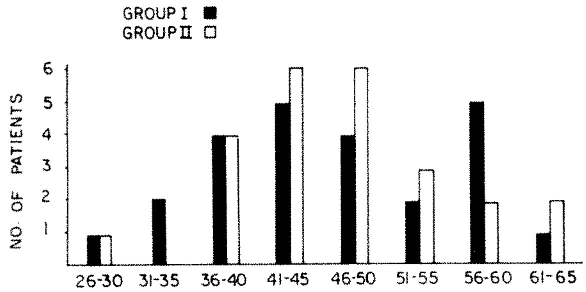

Fig. 1.
Age distribution of the patients.

TABLE I
Distribution of patients among rural and urban population

	Group I (5F/week)	Group II (1F/week)
Rural	14	17
Urban	10	7
Total	24	24

TABLE II
Early tumour regression

Degree of regression	Regression at the end of treatment		Regression 3 months after treatment	
	Group I	Group II	Group I	Group II
Incomplete	23	22	3	3
Complete	1	2	21	21

Results

Figure 1 shows the similar age distribution of patients in the two groups. Table I shows that in both groups the majority of the patients were from rural areas. Table II shows that both at the end of treatment and at three months, regression of the tumour was the same in both series. In the absence of pain, residual parametrial induration was not considered as residual disease. It is expected that with the passage of time and further follow-up some of these cases will develop frank recurrence. In group II patients, it was an impression that most of the tumour at the cervix had already regressed at the time of the intracavitary insertion. Another major advantage of large single fractions was the rapid control of bleeding. Excessive bleeding in the daily fractionation regime could be controlled easily by early intracavitary radium but this was sometimes difficult and occasionally unsuccessful on account of nonvisualization of the external os.

TABLE III
Early normal tissue reactions

	Group I	Group II
Moist skin reaction	3	2
*Severe diarrhoea	8	8

*Severe enough to interrupt treatment for more than one week.

Three patients in each of the groups were never free from tumour and died shortly after treatment. In both series one patient died from the effect of distant metastases with control of disease at the primary site. In group I, one patient died from recurrence, two years after treatment.

Early normal tissue reactions

Table III gives the early skin and bowel reactions in the two groups. Both were very similar and acceptable. Moist skin reactions occurred in obese patients. Diarrhoea was also more common in the obese.

The satisfactory early tumour regressions as well as the acceptable acute normal tissue reactions in the group II patients were very encouraging.

Late normal tissue reactions

Our hopes and expectations of having found a very satisfactory fractionation regime suitable for our patients were quickly demolished when late radiation reactions started developing in patients of group II, beginning seven months or more after the onset of radiation (Table IV). Soon every surviving patient developed a severe bowel reaction. The first indication in all was tenesmus and blood and mucus in the stools. Sigmoidoscopy revealed a haemorrhagic mucositis localized to a 10–12 cm length of rectosigmoid. In a few, there was an oedematous, indurated and ulcerated area on the anterior rectal wall which felt like tumour but never revealed malignant disease on histological examination. In only one third of the patients could these symptoms be controlled to a reasonable extent by medication with opiates, anticholinergics and corticosteroids. The latter were first commenced and continued as suppositories in those who benefited. In others, a short course of oral corticosteroids was used to assess its effect. In six, the blood and fluid loss was considered severe enough to warrant emergency colostomy. One of these patients died three months later with no clinical evidence of tumour. Another developed a perforation of the small bowel and a pelvic abscess and died following surgery. One patient died from the complications of a bilateral uretero-sigmoidostomy for a vesico-vaginal fistula, one year following treatment. Two patients developed rectovaginal fistulae with no evidence of recurrence. Both are refusing a colostomy and managing with opiates. In two obese patients there is extensive troublesome oedema in the field of radiation. In one, the oedema is extending to the legs. In both there is as yet no clinical evidence of residual or recurrent disease.

In the group I patients all of whom have been followed up for over two years as against the minimal follow up of one year in group II, 11 patients are alive and well with no symptoms of bowel reaction (Table IV). Another eight are surviving in whom proctitis lasted over six months. It is quite possible that in some a resultant stricture may require a colostomy at a later stage. A similar fate is expected in some of the eight patients of group II in whom proctocolitis has persisted for over six months. So far none of the 24 patients of group I has required a colostomy for proctitis, stricture or fistula. In our previous experience with this regime of giving a total dose exceeding 6000 rad to the rectum, about 5% required surgical intervention to control the late bowel complications.

The late bowel reactions following the single weekly fraction technique are so severe and unacceptable that these have prevented us from doing a further random prospective trial using this regime.

DISCUSSION

There was no relationship between the early radiation reactions arising during the course of treatment and immediately following it and the development of late complications seven months or more after radiation. According to Buchler *et al.* (1971) there is a definite relationship between the severity of early bowel reactions and subsequent complications involving the gastrointestinal tract. They have, however, reported that among 16 out of 410 patients who later developed gastrointestinal or genito-urinary fistulae, only seven had earlier developed moderate to severe bowel reactions. Similarly, out of 33 patients developing a stricture of the recto-sigmoid, only 15 had been preceded by moderate reactions during treatment. So it is not difficult to draw an opposite conclusion from their statistics.

Eighty-five per cent of our patients come to us with parametrial involvement out to the pelvic wall—stage III (UICC) or stage IIIB. When it became possible to give a higher dose with cobalt 60 teletherapy, treatment giving a total dose of 8000–8500 rad to point A and 6000 to the pelvic wall was commenced in 1965. In the first plan, 6000 rad was given by cobalt 60 teletherapy to the whole pelvis and this was followed by a radium insertion. In the second plan 6000 rad was given to point A with radium and the remaining dose to point A and parametria by cobalt 60 teletherapy. In the latest plan the contribution of dose to point A was 4000 rad by intracavitary insertion and 4000 rad by cobalt 60 teletherapy. Although no proper follow up was done of the first two regimes, the impression was that both were equally good. A few patients developed bed sores after the single large radium insertion delivering 6000 rad to point A. Similarly a number of patients developed subcutaneous oedema when 6000 rad was given by cobalt 60 teletherapy. The third regime of 4000 rad by intracavitary insertion and

TABLE IV

LATE REACTIONS OR COMPLICATIONS

Complications	Group I (5 fractions per week) (minimum follow up 24 months)	Group II (1 fraction per week) (minimum follow up 12 months)
No complications	11	0
Proctitis lasting over 6 months	8	8
Severe proctitis requiring colostomy	0	6 (1 dead*)
Perforation of small bowel	0	1 (dead*)
Vesico-vaginal fistula	0	1 (dead*)
Rectovaginal fistula	0	2
Oedema of vulva, mons, etc.	0	2
Residual disease	3 (dead)	3 (dead)
Died from metastasis	1 (lung)	1 (liver)
Died from local recurrence	1	0
Total	24	24

*Died after surgery.

4000 rad with cobalt 60 teletherapy was free from both these drawbacks and became the treatment policy in 1972. Cowell (1953) reported a complication rate of 59.5% when a dose of 4500–5500 rad to point A was given with radium supplemented by 4000 rad from external radiation in four weeks. With deep X-ray therapy, this dose was much higher than the dose received by our group I patients. Frick *et al.* (1960) used a similar dose to our group I patients and reported four deaths and five major complications in 65 patients. Deeley (1954) reported proctitis and other late complications in 55% of patients when the rectal dose was above 5400 rad.

Buschke (1964) stated in his concluding remarks at a symposium on protraction and fractionation: "Sufficient prolongation of the overall treatment time is the most important factor from the point of view of preservation of normal tissues, particularly vasculo-connective structures . . . details of fractionation during such protracted periods of overall time appear to be of less importance and in part adjusted to practical and economic considerations without jeopardising the results". Alper *et al.* (1962) concluded that the "shoulder" of survival curves with an extrapolation number greater than one, indicated a decreasing efficiency of irradiation when administered with increasing fractionation. Sambrook (1964) also reached the same theoretical conclusion that higher extrapolation numbers indicate the desirability of delivering the dose in fewer larger fractions. In addition to the economic desirability of using fewer fractions, we expected to see better tumour control with similar complications by using doses with the same NSD and cumulative radiation effect (CRE). As pointed out earlier the dose selected for one fraction per week was calculated from TDF tables of Orton and Ellis (1973). Using the NSD formula, 4000 rad in 20 fractions over 26 days has an NSD of 1361. 2900 rad given in five fractions over 28 days has an NSD of 1367. Exactly similar figures are obtained when cumulative radiation effect is calculated for the two regimens using the CRE formula of Kirk *et al.* (1971). So the two regimens should be iso-effective if the three formulae predict correctly.

Having selected our dosage in this manner, we had not expected to see the severe late reactions reported by Sambrook *et al.* (1950), Sikov *et al.* (1963) and Atkins (1964a and b) following their once-weekly fraction regimes. Sambrook *et al.* (1950) used the same total dose with once a week fractionation as in the daily fractionation schedules. Atkins (1964a) used 3250 rad divided in three weekly fractions for extensive head and neck tumours. Using similar high weekly fractions for inoperable breast carcinomas he reported a high percentage of late fibrosis involving pectoralis musculature as well as radiation myelitis, making him discontinue the project despite an excellent tumour response (Atkins, 1964b). We were expecting that iso-effect doses would hold true for skin as well as for the bowel mucosa, and a regime of a few large fractions gave a theoretical possibility of achieving better tumour control in stage III cervical carcinoma. We agree with Fletcher *et al.* (1958) that there is no evidence of absolute levels for the radiation tolerance of bladder and rectum. Within the range of 6000–6500 rad to the rectum we did not find any relationship between bowel complications and rectal dose in group I. The total dose of 8000 rad to point A and 6000 rad to the pelvic wall and parametria had been giving an acceptably low rate of late major complications in the last 11 years and so this dose was chosen as our standard.

It is possible that some modification in dose is required for fewer fractions involving large volumes of bowel mucosa. It is worth noting that the acute bowel reactions during the course of treatment and immediately following it were similar to those occurring with five fractions per week. The vasculo-connective tissue of the bowel wall did not tolerate these high dose fractions and produced late complications. Wiernik and Perrius (1975) reported that progressive diminution of pericryptal fibroblasts may be a component of late radiation damage in rectal mucosa and warn that it is necessary to show that late radiation damage caused by a revised fractionation schedule is not excessive. It is apparent that the dose fractionation schedule used by us is unacceptable. It is quite possible that another dose fractionation pattern may turn out to be better.

Large single weekly fractions with the same NSD and CRE values as the five daily fractions per week are not tolerated by the rectosigmoid.

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Book review

Textbook of Radiologic Technology. By C. A. Jacobi and D. Q. Paris, 6th edn. pp. x + 559, illus., 1977 (U.S.A. C. V. Mosby Co.; London. Henry Kimpton), £14·25.

New student radiographers and trainee radiologists are faced with reading several standard textbooks and selected passages from a multitude of other publications. This book, of modest size, written by two American technologists, represents an attempt to include all this basic information in one volume.

The contents are divided into 13 chapters, an appendix and a glossary of terms. Each chapter ends with a group of 20 to 40 related questions. The first five chapters comprise an introduction to radiography, basic physical science, the production of X rays, radiographic production and radiation therapy and medical uses of radioactive isotopes. The following three pairs of chapters deal with regional anatomy followed immediately by the corresponding radiographic positioning. Chapter 12 is entitled Anatomic Physiology and is followed by the largest single chapter which deals with contrast studies. All sections of the book contain abundant illustrations, including clear line diagrams and photographs which are of uniform high quality reproduction. There is a good index which is easy to use.

The pressures on space have inevitably resulted in a rather superficial treatment of many of the subjects including tomography, phototimers and image intensification. Many topics have been omitted, including radiography of the radial head, the dislocated shoulder and the subtalar joints. There is no account of portal venography, radiculography, or renal puncture. The description of skull views does not include the use of a skull table. Some of the techniques do not conform to standard British practice. For excretion urography a test dose is recommended, a film of the nephrogram stage is omitted and ureteric compression is advocated immediately after the injection. The suggestion that the syringe should be filled with contrast medium by the radiographer will not be widely accepted.

Despite these reservations, the book provides an excellent introduction to the whole subject of radiography and allied basic sciences. It is well-presented, clearly printed on good quality paper and has an excellent binding. It should be recommended to the budding radiographer or radiologist at the start of their careers and will provide a sound overview of the whole subject which will facilitate further detailed study. It should be available in all training schools for radiography and radiology.

W. M. Harrison.

1978, *British Journal of Radiology*, *51*, 363–369 May 1978

Further experience with radiotherapy by multiple daily sessions

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Abstract

Since 1972 over 100 patients have been treated by frequent daily sessions of radiotherapy with a short overall time. Cobalt 60 teletherapy and 250 kV X-ray beams have been used with radical or palliative dosage. The tolerance to these regimes of the skin, breast, chest wall, neck, lung and pelvis is discussed and the tumour responses described.

Radiotherapy by multiple daily sessions is clinically possible and often an advantage. Its therapeutic ratio is not inferior to comparable regimes using longer intervals.

Radiobiological research has predicted the potential of frequent fractionation (Fowler *et al.*, 1963). If fractionation is better than single exposure, then it is likely that some types of fractionation may be better than others. Different regimes using anything from one to five fractions a week have been tried with the only apparent advantage an administrative one. The advantage of the split-course introduced by Sambrook (1962) was that it caused a reduction in acute reactions. Pierquin (1970; 1974) attempted to simulate low dose-rate radiation by frequent small fractions, and the possible advantages of small fractions were explored by Baclesse (1955), and more recently by Littbrand (Backstrom *et al.*, 1973; Jakobson and Littbrand, 1973; Littbrand *et al.*, 1975) and by Simpson and Platts (1976) who used three daily sessions. Shukovsky *et al* (1976) attempted twice-a-day fractionation.

In short courses of treatment lasting for five days repopulation does not play a role (Denekamp and Harris, 1976), but intracellular recovery is fast and allows frequent sessions. A very short course can still preserve the advantage of fractionation only if there is a different rate of repair of sublethal damage between normal tissue and the tumour. A preliminary report of our experience with multiple daily sessions has appeared already (Svoboda, 1975).

Patients and Treatment Schedules

From October 1972, multiple daily sessions of radiotherapy (referred to below as MDS RT) were used in the treatment of several types of malignant tumour.

Breast carcinoma

Thirty-nine patients were treated between 1972 and 1975 for local recurrence, inoperable primary tumour or post-operatively by cobalt 60 teletherapy with tangential fields. The treatment was delivered in three or four daily fractions, at 9 a.m., noon, 3 p.m. and 6 p.m., on five days per week. Both fields were treated at each session and 15–30 fractions were delivered in 5–12 days. In three patients, 250 kV X-rays were used with similar fractionation.

Squamous carcinoma of larynx and hypopharynx

Thirteen advanced cases with a poor chance of cure by conventional methods were treated between 1973 and 1975 by cobalt 60 with opposed fields covering the larynx or hypopharynx and sometimes also the adjacent lymph nodes. Treatments were given on five days per week, so that 24–34 fractions in three daily sessions were applied in 10–12 days. The total dosage was 5000–5500 rad.

Bronchial carcinoma

Eighteen patients were treated between 1974 and 1975. Five had squamous carcinomas, two adenocarcinomas and five undifferentiated carcinomas. In six the diagnosis was only clinical. All the lesions were inoperable and advanced but only three patients had evidence of extrathoracic tumour extension. Two were treated by a three field plan, one by a single field and the rest by an opposed ^{60}Co pair. Two,

TABLE I

NSD values of the multiple daily sessions regimes used for the treatment of bronchial neoplasms

Number of Fractions	10	15	20	30	40	Time in days
Tumour dose						
2500	1210					5
3000		1310				5
3500		1530	1430			5
4000				1350		12
4500		1970	1840			5
5000				1680		12
5250					1650	12

three or four daily sessions were used over a total time of four to 12 days with a week-end pause. Ten to 40 fractions were delivered and all fields were treated at each session. The minimum interval between the daily sessions was three hours. Typical regimes and their NSD values are listed in Table I.

Bladder carcinoma

Four patients with T4 and six patients with T3 transitional cell carcinomas were treated between 1975 and 1976. Two patients with T3 tumours were treated pre-operatively by an opposed ^{60}Co pair delivering 3500 rad in 15 fractions over five days. The rest were treated palliatively by three fields of ^{60}Co teletherapy with the following dosage: 4000 rad in 15 fractions over five days, 4000 rad in 30 fractions over 12 days, 4500 rad in 30 fractions over 15 days, 4750 rad in 30 fractions over 15 days, 4500 rad in 40 fractions over 18 days, 4080 rad in 30 fractions over nine days, 3600 rad in 21 fractions over seven days. One patient did not finish the course.

Tumours of the pelvis and abdomen

Two recurrent ovarian adenocarcinomas, one adenocarcinoma of the colon, one recurrent squamous carcinoma of the vagina, one carcinoma of the prostate and one squamous cell carcinoma of the anus were treated between 1973 and 1976 by ^{60}Co teletherapy using two or three fields. 15–40 sessions over a period of 5–18 days in two, three or four fractions daily were used to deliver tumour doses of 3750–5250 rad.

RESULTS

Breast carcinoma

No systemic reactions were observed. Without bolus, there was either no early skin reaction or minimal erythema, whereas the use of full bolus or 250 kV X rays produced moist desquamation. The grading of early skin reactions is explained in Table II. Late changes appeared after four months, and at 18 months these were fully developed in the form of fibrosis and skin leathering. A dose of 4000 rad administered in 15 fractions over five days led to no such changes. However, 4500 rad applied by the same fractionation produced only moderate late changes, and no late changes at all if 24 fractions were used (Table III). If the MDS RT is applied after previous conventional daily radiotherapy, 3500 rad tumour dose in 17 and 3750 rad in 15 fractions are still tolerated well. Higher doses in 15 fractions over five days lead to late damage. All the late changes were asymptomatic and there was no skin or bone necrosis due to radiation, and no pulmonary fibrosis was seen.

TABLE II

ARBITRARY SCALE OF EARLY SKIN REACTIONS

Reaction increasing	Reaction regressing	Code
No reaction	No visible change	0
Just noticeable erythema	Mild pigmentation	1
Erythema	Pigmentation, atrophy	2
Intensive erythema	Dry scab	3
Moist spots	Moist spots and crusting	4
Confluent moist reaction		5

The tumour response was usually fast. In several cases it was already noticeable during the course of treatment. The results are summarized in Table IV. Apart from the group of inflammatory carcinomas where the response was disappointing, only one tumour failed to regress, and the lesions disappeared completely in 14 cases. Considering the advanced character of the disease in most of these patients, the tumour response was very good.

Carcinoma of the larynx

Acute mucosal reactions appeared in the second week of treatment and culminated in a fibrin coating during the third or fourth week. Subjective symptoms were mild; only one patient with a post-cricoid carcinoma suffered severe dysphagia. The reactions healed at the end of the second month or earlier. Erythema was the only early skin reaction. The primary tumour regressed in 11 out of 13 patients (Table V). Four lesions recurred locally. Two patients had a laryngectomy six months after radiotherapy and both are well. Ten patients survived a year or more and six of them are alive without recurrence at 35, 30, 26, 21, 12 and 12 months. Only the patient with a post-cricoid carcinoma developed laryngeal and upper oesophageal fibrosis which required a tracheostomy and temporary gastrostomy. In one patient who died of metastatic disease, post-mortem examination showed only moderate post-radiation laryngeal changes and no local disease. Another patient died of aspiration pneumonia and post-mortem examination revealed severe radiation changes with ulceration of the epiglottis and cartilage necrosis. Active disease was present only in the cervical lymph nodes. Similarly, one of the laryngectomy specimens with necrotic cartilage had only moderate radiation changes and did not contain active disease, although this had been present in the cervical lymph nodes. The second laryngectomy specimen contained tumour infiltrating the laryngeal cartilage and there were severe radiation changes near the tumour but only moderate changes away from it. One of the patients has mild, unilateral and asymptomatic posterior neck fibrosis. Similar fibrosis developed between five and 14 months in another patient who had this area included in the treated volume.

Six more-recently treated patients with less advanced vocal cord carcinoma (T1 or T2, three of whom are recorded in the Table) responded well and in August 1977 are tumour and symptom free at 29, 19, 19, 10, 6 and 6 months.

Carcinoma of the bronchus

The systemic tolerance of all the regimes was good. Six patients complained of moderate and temporary dysphagia and three out of six (who survived six months) developed post-radiation

TABLE III

Carcinoma of the breast

The tolerance of skin following large volume radiotherapy by multiple daily sessions

Fractions X dose per fraction	Tumour dose (rad)	Total time in days	NSD	Build up	Acute skin reaction (< 8 weeks)	Late skin changes (6–18 months)
			250 kV X rays			
15 × 250	3750	5	1820*	bolus	4–5	Skin atrophy and telangiectasia
			^{60}Co teletherapy			
15 × 266	4000	5	1750	0	1	0
15 × 283	4250	5	1860	0	0–1	0 or minimal pigmentation at 6–27/12
15 × 300	4500	5	1970	0	0–1	Leathering and fibrosis after 1 year
115 × 300	4500	5	1970	Full bolus	4–5	Atrophy and pigmentation, fibrosis
20 × 237	4750	5	1940	2 mm vaseline gauze	2 (skin folds 4)	Skin and muscle fibrosis and atrophy after 7 months
15 × 317	4750	9	1950	0	1–2	Moderate fibrosis at 18 months
24 × 198	4750	9	1740	vaseline gauze	2	0 at 2 years
30 × 150	4500	12	1510	0	1	0 at 1 year
			MDS RT after previous daily ^{60}Co teletherapy, 6000 rad TD in 50 sessions over 70 days			
17 × 205	3500	5	1490	0	0	0
15 × 250	3750	5	1640	0	0	0 at 11 months
15 × 266	4000	5	1750	0	0	Fibrosis at 14–20/12, at 36/12 softening
15 × 273	4100	5	1790	0	0	Leathering and fibrosis 10–31/12
15 × 280	4200	5	1840	0	0	Leathering and fibrosis 17–27/12
21 × 202	4250	11	1570	0	1	Fibrosis at 16 months

*With allowance for RBE of 250 kV X rays relative to ^{60}Co γ rays (1/0.9).

TABLE IV

Carcinoma of the breast
Tumour response to radiotherapy by multiple daily sessions

Local condition	Response	Number	Month of reactivation or local recurrence	Last seen without recurrence or reactivation (in months)
T4b, c	Full	7	4, 11, 11	21, 21, 26, 26
	Partial	10	2½, 4, 4, 4, 5, 6, 7, 7, 21	27 (radical surgery at 8)
T3b, T2a	Full	2	8	24 (radical surgery at 3)
T1 (pre-op.)	—	1	—	7
Post-operative	Prophylatic	1	—	34
Local recurrence after previous MV RT	Full	3	8	31, 39
	Partial	6	4, 5, 7, 10, 11, 22	—
	Nil	1	—	—
Inflammatory carcinoma	Partial	2	11	5 (longest survival 1 yr.)
	Minimal or none	4	Residual	— (2 died less than 1 month after RT)
Repeated MDS RT for T4 tumours	1st: Full	1	5	—
	2nd: Partial		3	—
	1st: Partial	1	7	—
	2nd: Partial		—	26 no reactivation
All		39		

Summary: Full response 15
Partial response 19
Nil 5

fibrosis in the treated volume. A chest radiograph showed full tumour response in eight and partial tumour reponse in five patients. Five tumours either did not respond or it was not possible to assess the response. Six patients lived between six and 12 months and two survived one year. On 31.12.76, two patients were alive, one and six months after the treatment. Fifteen of 16 patients probably had active disease at the time of death, but 11 out of 18 were known to have distant metastases. Local disease caused death only in four patients.

Bladder carcinoma

All patients with transitional cell carcinoma of the bladder developed diarrhoea which commenced between five and 15 days after the first session and settled before 40 days. With a dose of 4000 rad, one patient also complained of proctitis. Two patients had a total cystectomy two days after the completion of pre-operative treatment. One of them died one month later due to a pulmonary embolus; the other patient developed superior vena caval obstruction caused by another bronchial primary ten months later. He also had mild chronic diarrhoea following treatment. Of the remaining eight patients, two have shown good early tumour response, four failed to respond and two await cystoscopy. The longest survival is 11 months.

Tumours of the pelvis and abdomen

There was no response from two advanced carcinomas of the ovary. A dose of 4250 rad in 26 fractions over 18 days caused proctitis but 3750 rad in 30 fractions over 15 days caused no symptoms.

A fast decompression of ureters in a uraemic patient with carcinoma of the prostate was not achieved. 4250 rad in 30 fractions over 14 days caused enteroproctitis in the second and third week after the beginning of treatment. There was also no response of an adenocarcinoma of the anus and

TABLE V

Squamous cell carcinoma of the larynx and hypopharynx
Results of multiple daily sessions radiotherapy by ^{60}Co teletherapy, two fields 5 × 5 – 5 × 10 cm
5500 rad, 24 fractions in 10 days = 2000 ret
5500 rad, 34 fractions in 12 days = 1800 ret

Primary tumour (site)	Age	TNM	Fractions	Tumour Dose	Time in days	Tumour response or local recurrence (months)	Further treatment (months)	Follow-up in months		
								Alive	Died	Comment
Ary-epiglottis	48	T4N1M1	24 × 230	5500	10	Full	RT, lung	—	30	PM larynx-moderate RT changes. Lung metastasis.
Ary-epiglottis	70	T3N1M0	30 × 183	5500	11	Full	—	—	9	PM necrotic primary. Tumour in the neck lymph nodes.
Epiglottis	71	T2N1M0	27 × 185	5000	10	Local rec. (8)	—	—	16	
Larynx	67	T3N2M0	24 × 219	5250	10	Full	Laryngectomy and block (6)†	26	—	No recurrence.
Vocal cord with sub-glottic ext.	77	T2N1M0	24 × 208	5000	10	Local rec. (8)	Refused	—	28	
Vocal cord with sub-glottic ext.	75	T2N0M0	34 × 162	5500	12	Local rec. (10)	Chemotherapy	—	15	
Vocal cord with sub-glottic and tracheal extension	73	T4N0M0	26 × 192	5000	13	Residual	Laryngectomy (6)‡	35	—	No recurrence.
Vocal cord	81	T2N0M0	27 × 204	5500	11	Full	—	21	—	Symptom free.
Vocal cord	72	T2N0M0	30 × 183	5500	12	Full	—	12	—	Symptom free.
Vocal cord	73	T2N0M0	30 × 183	5500	12	Full	—	12	—	Symptom free.
Hypo-pharynx	68	T3N3M0*	30 × 167	5000	12	Residual	—	—	3	
Post cricoid	57	T2N0M0	28 × 188	5250	10	Full	Gastrostomy (temporary) and tracheostomy	30	—	Fibrosis of larynx and oesophageal stricture
Pyriform fossa	72	T2N0M0	30 × 175	5250	12	Local rec. (7)	—	—	11	Broncho-pneumonia

*Patient had also metastatic breast carcinoma.
†Primary tumour was devitalized, radiation changes moderate, cervical lymph nodes positive.
‡Active primary tumour and severe radiation changes were present.

rectum in a patient who received 5250 rad in 27 fractions over 11 days to a small volume. Extensive recurrence of an adenocarcinoma of the colon treated with large volume irradiation of the abdomen delivering 4000 rad in 20 fractions over five days resulted in malaise and nausea in the week after the completion of the treatment. The tumour then partially regressed and the patient was symptom free for three months. The only full response noted was in a patient with a recurrent squamous cell carcinoma of the vagina, which was treated with 4750 rad in 15 fractions over 24 days (three fractions per day, with a five day gap after the first seven treatment days). This patient developed enteroproctitis in the second and third week but was symptom free a month later and eventually died ten months later of upper abdominal disease without local recurrence.

GENERAL DISCUSSION AND CONCLUSIONS

It is possible to deliver relatively high doses in multiple daily sessions over five days to a large volume of chest wall because of the fast intracellular recovery during the three hours between sessions. There is a plateau effect at approximately 20 fractions. Further increase in the number of fractions in a five day course improved the tolerance only marginally. Conversely, we can say that the plateau effect is obvious when the dose per fraction is 250 rad or less (Dutreix and Wambersie 1976; Wambersie *et al.*, 1974). Cohen (1972) predicts that the difference in tolerance between a course of 15 fractions given in five days, or the same 15 fractions given in ten days, is small and is caused by the weekend gap and repopulation.

The tumour response of advanced breast carcinomas would probably not have been better after conventional daily fractionation lasting three to ten weeks. The speed of tumour regression and the good systemic tolerance makes MDS RT suitable for palliative radiotherapy, and also for pre- or post-operative regimes especially in patients where hospitalization is desirable or necessary. Radical treatment by a ten-day MDS RT course can also be used with advantage in carcinoma of the larynx. It produced only moderate early and late reactions which were tolerated even by elderly patients. Symptomatic late changes occurred only in one patient with a post-cricoid carcinoma. There was no noticeable difference in the mucosal reactions to 5500 rad in ten to 12 days, delivered in 24 or 34 fractions. This is probably due to the plateau effect which limits the advantage of superfractionation for the short overall time regimes.

The acute systemic tolerance and early tumour response of bronchial neoplasms were encouraging. Good but short palliation was achieved.

Frequent fractionation did not have any special advantage for the treatment of advanced transitional cell carcinomas of the bladder or adenocarcinomas of the intestine or ovary. MDS RT causes enteroproctitis at doses above 3000 rad in 15 fractions over five days. 4000 rad in 15 fractions over five days is probably the limit of tolerance. Doubling the number of fractions or the overall time did not reduce the symptoms.

It is possible to reduce the interval between treatment sessions to three hours during a working day and thus deliver a full dose of radiotherapy in five or ten days which preserves the advantages of fractionation. As the repopulation in five days is negligible, the rate of repair of sublethal damage in normal tissue and in the tumour must differ. Doses of 4000 rad in 15 fractions over five days, or 4750 rad in 24 fractions over ten days cause no late changes, even when a large volume is treated. Such regimes are especially advantageous in hospitalized patients but can also be administered to out-patients. This new fractionation technique provides an option for tailoring the treatment to the individual tumour.

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Book review

Radiation protection design guidelines for 0.1–100 MeV particle accelerator facilities: NCRP report No. 51, pp. vii+159, 1977 (National Council on Radiation Protection and Measurements, Washington) $5.00.

The purpose of this report is to provide design guidelines for radiation protection in particle-accelerator facilities. Although it is claimed to be directed mainly at designers, it could profitably be read by anyone concerned with the operation and radiological protection problems of accelerators. As a practical text-book it gives full coverage to all safety aspects and provides rule-of-thumb guidance together with excellent summaries of relevant data. It is a great pity therefore that the document is marred by some ineptness in handling the concepts of radiological protection. In one or two places the distinctions between dose and dose rate or between dose-equivalent and dose-equivalent index are lost. Of particular concern is a definition of dose-equivalent rate which includes an occupancy factor, such that the dose-equivalent rate in an area with an occupancy factor of 0.1 would be defined as this fraction of the instantaneous dose-equivalent rate.

In one respect the document departs from the concepts of ICRP and from the basic safety standards of the European Communities. The distinction made by both ICRP and the CEC between controlled areas where the dose may exceed three-tenths of the annual maximum permissible limits and supervised areas where it may be between one and three-tenths is not recognized. Instead only controlled areas where the dose equivalent rate may be up to 2.5 mrem h^{-1} and non-controlled areas where it may be up to 0.25 mrem h^{-1} are proposed.

One of the many appendices is devoted to definitions. While these are appropriate for their use in the text, many would not be acceptable for general use. Another appendix is devoted to dose limits and uses terms such as "retrospective annual limit", "fertile women" and "population dose limits" which can only be properly understood if the recommendations of ICRP are consulted. The same appendix includes a table of neutron fluence rates per unit dose-equivalent rate which is at variance with ICRP publication 21.

In summary the report provides excellent practical guidance but needs to be supplemented by a working knowledge of ICRP recommendations and specific statutory requirements.

J. A. Dennis.

1978, *British Journal of Radiology*, *51*, 370–374

The complication probability factor: a method for selection of radiation treatment plans

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ABSTRACT

The problem of selecting the best radiation treatment plan from several that may offer subtle differences has been considered. A method is introduced in which the concept of a complication probability factor (CPF) can be used to quantify the relative merits of such treatment plans. The CPF is a variant of integral dose and consists of a weighted volume of irradiated normal tissue which may relate to radiation-related complications. Treatment plans for irradiation of a pelvic tumour volume using parallel opposed, 360 deg rotational and four-field techniques with X-ray beams of 4, 8, 22, and 45 MV have been analyzed to demonstrate the utility of the method. This analysis suggests that complex radiation delivery techniques may offer a substantial improvement in dose distribution characteristics, while higher beam energies are relatively less advantageous.

At present, there is no generally accepted basis for selecting the best treatment plan from the various available possibilities. Current practice relies primarily on clinical judgement to make this decision. With the development of methods for complex three-dimensional treatment planning and radiation delivery, an increased number of alternative plans may become available. These plans may contain subtle differences in dose distribution that may have clinical significance. In addition, the variety of energy capabilities of modern super-voltage equipment may further contribute to the number of plans from which selection is required.

Selection could be assisted by developing a quantitative method of plan evaluation which would place numerical values on the relative merits of various treatment plans. These values would then be available as an aid to the clinician in selection of treatment plans and subsequent evaluation of therapeutic results. Using clinical data and radiobiological principles, we propose such a quantitative method for plan analysis. As an example, the method is applied to the problem of radiation therapy of the pelvis for cervical carcinomas. The effects on dose distribution of variations in radiation energies and external beam delivery techniques are considered.

THEORETICAL BASIS

The probabilities of both tumour control and radiation-related complications are a function of dose, time, volume, histological and radiobiological factors. If established time-dose relationships are maintained, radiation treatment volume may be the limiting variable in determining the therapeutic ratio. Clinicians have long known that a relationship exists between dose and volume and the incidence of radiation complications and have employed general guidelines for limiting dose and field size in clinical practice.

There is experimental evidence that radiation effects for a given dose are volume dependent. Allen and Freed (1956) and Von Essen (1960, 1963) established the relationship between radiation necrosis and treatment field size for skin cancer. Shukovsky and Fletcher (1973) analyzed complications due to necrosis in the treatment of head and neck tumours, observing a relationship between field size and incidence of complications. Stockbine *et al.*, (1970) reported the results of external beam therapy to the whole pelvis with doses greater than 3000 rad for pelvic cancer and observed a high complication rate. Allt (1969) compared the results of pelvic irradiation for carcinoma of the cervix with ^{60}Co and 22 MeV betatron, observing an improved survival and fewer complications in the treated patients with the betatron. He suggested that the difference was the result of delivering radiation more effectively to the tumour volume with the betatron. Although these examples provide supporting evidence for a dependence of radiation complications on treated volume, the exact nature of the relationship is unknown.

The dependence of complication incidence on dose is better established. Although actual clinical data are limited, a Holthusen type of dose response relationship is believed to exist (Strandquist, 1944; Fletcher and Shukovsky, 1975). It is reasonable to assume a sigmoid curve for the available data on complication probability versus dose.

A concept which may relate complication probability to dose and volume is that of integral dose. Although the use of tissue-specific integral doses has not been adequately investigated, correlation with clinical experience has generally been unsatisfactory (Mayneord, 1942; Johns and Cunningham, 1969;

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Johns, 1976). We propose to use a variation of the integral dose concept to formulate a quantitative basis for selection of radiation treatment plans.

The method can be applied to treatment plans which have equal probabilities of tumour sterilization, by meeting boundary conditions such as minimum tumour dose, degree of inhomogeneity and maximum doses to critical structures. Such plans generally demonstrate differences in the volume of normal tissue irradiated to a high dose and this is assumed to relate to differences in radiation-related complications. As a first approximation, a linear dependence is assumed relating complications to volume of normal tissue irradiated, if the doses vary over a limited range and volume increments are small. Clinical data can be used to fit a Holthusen type of curve for complication probability as a function of dose. A complication probability factor (CPF) can then be calculated, and the plan with the smallest probability of producing complications for given probability of cure is selected as the "best" plan.

SAMPLE SOLUTION

Several conventional plans for treatment of carcinoma of the uterine cervix have been selected to demonstrate the utility of this method. Clinical data are available to provide estimates for some of the parameters under consideration, including control rates, complication rates and tumour volume.

The following assumptions are made in the analysis:

1. The tumour volume is defined on an anatomical basis. Parallel opposed anterior-posterior (AP–PA), rotational and four-field (box) treatment techniques each achieve the same probability of tumour sterilization if a given minimum tumour dose (TD) is achieved.
2. Tumour dose inhomogeneity is limited to 15% above the specified TD minimum.
3. The effect of radium is not included in the analysis. Assuming a fixed type of application, the dose contribution of radium is relatively constant for each plan. If there are significant differences in the application of radium, a method of mixing external beam and radium contributions should be used.
4. Normal tissue outside the tumour volume is considered the basis for minimizing radiation-related complications. The pelvic and lower abdominal contents are considered to be of a uniform composition from the standpoint of complication probability.
5. "Matrix" tissue (normal tissue within the tumour volume) is not significant in differentiating between radiation-related complications, since all plans treat it to a similar dose.
6. Complication probability obeys a sigmoid dependence on dose and is linearly dependent on volume.

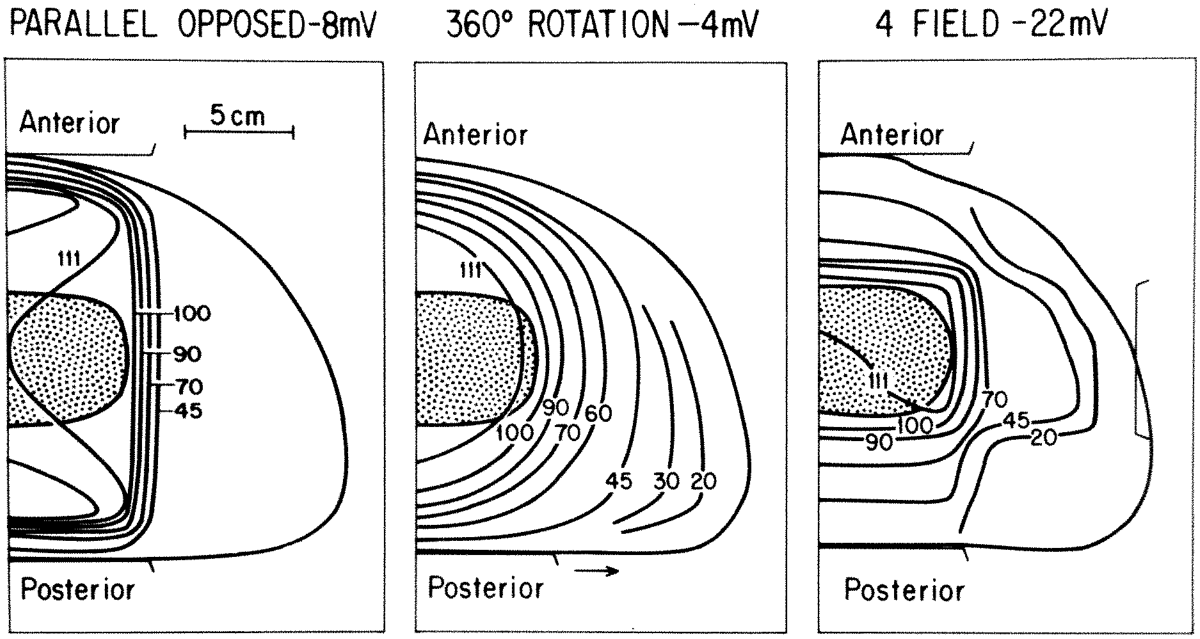

FIG. 1.

Representative plans for parallel opposed, 360 deg rotation and four-field treatment techniques.

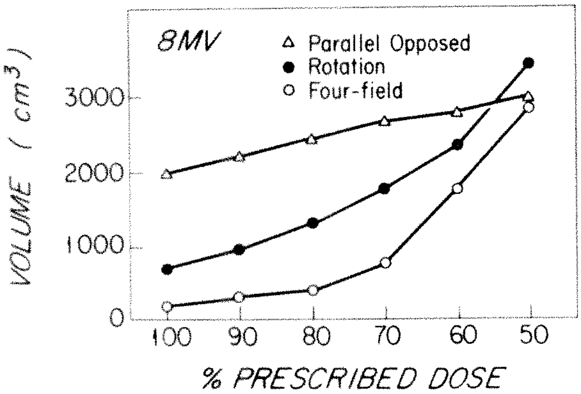

Fig. 2.

Estimated volume achieving a minimum percentage of the prescribed dose for 8 MV as influenced by treatment plan variations.

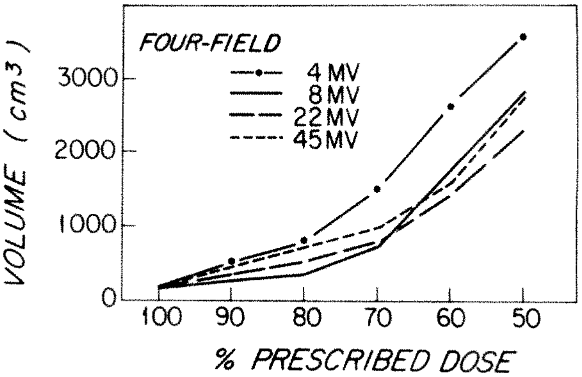

Fig. 3.

Estimated volume achieving a minimum percentage of the prescribed dose for the four-field plan as influenced by energy.

7. The therapy equipment of various energies is assumed capable of 360 deg rotation about an isocentre.

With these assumptions, the complication probability factor (CPF) can be defined as:

$$\mathrm{CPF} = \sum_{i=0}^{1.0} P_{\mathrm{Di}}(V_{\mathrm{Di}})$$

where P_{Di} is the probability of complications at a specified dose level Di (Fig. 4) and V_{Di} is the volume of normal tissue receiving dose Di (Figs. 2, 3). Exact data for the dose-response curves are not necessary, since only relative complication probabilities are determined for a given anatomical location. From such considerations, the treatment plan with the smallest calculated CPF would be the plan least likely to produce radiation-related complications when other boundary conditions are met.

An idealized patient contour was used in the calculations. An anterior to posterior separation of 21 cm was assumed and a cylindrical tumour volume of 1000 cm^3 was selected as the volume at risk for carcinoma of the cervix. An Artronix PC–12 computer was used to simulate three radiation treatment plans: parallel opposed fields (AP–PA), 360 deg. rotational, and four-field (box) treatment techniques as illustrated in Fig. 1. Other treatment techniques such as lateral arcs and double isocentric rotations have not been considered in this analysis.

Dose distributions were calculated for 15 × 15 cm anterior and posterior static and rotational fields and 9 × 15 cm lateral fields. In addition, plans were calculated for the maximum inhomogeneity within the tumour volume for each of the techniques. Beam energies of 4, 8, 22, and 45 MV were selected. Depth dose distributions for the 4 and 8 MV beams were based on linear accelerator data and the distributions for the 22 and 45 MV beams on betatron data.

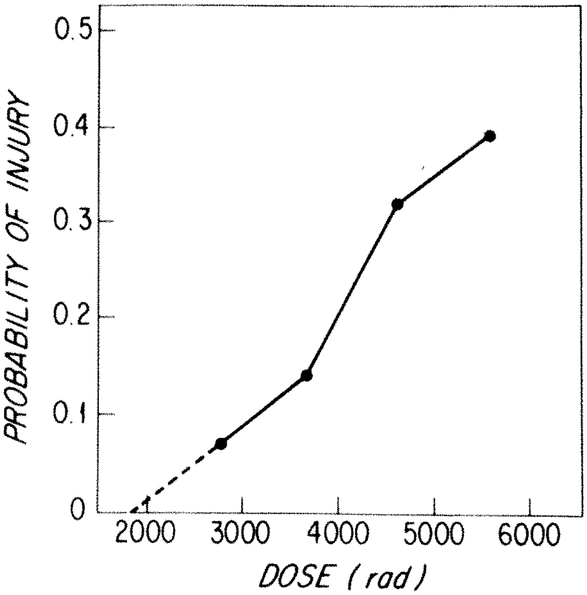

Fig. 4.

The probability of radiation-related injury to the gastro-intestinal tract. The line approximated from data by Friedman (1952). The broken line is an extrapolation.

Isodose contours were normalized to 100% for the minimum tumour dose and inhomogeneity within the tumour volume was limited to a maximum of 15%. Using a polar planimeter, direct area readings were obtained from the isodose contours and formed the basis for estimates of volumes

TABLE I

COMPLICATION PROBABILITY FACTORS (CPF) AS A FUNCTION OF ENERGY AND TYPE OF PLAN

Energy	CPF values		
	Parallel opposed	360 deg rotation	Four-field
4 MV	839	610	474
8 MV	857	567	319
22 MV	649	416	286
45 MV	793	554	355

achieving the indicated dose levels. These volumes are plotted against percent of prescribed dose in Figs. 2 and 3 to illustrate the effects of plan selection and beam energy.

Figure 4 is an adaptation of data for the incidence of various radiation complications of the gastrointestinal tract as a function of dose (Friedman, (1952). We have elected to use a point-to-point relationship, although a straight line approximation might be satisfactory within our limits of knowledge. These data were used to estimate incremental volume contributions to the complication probability in the calculation of CPF values for each plan as shown in Table I. The greatest differences in CPF values are observed when radiation treatment techniques are varied, the box technique offering the minimum volume of normal tissue irradiated to a high dose. The effect of varying radiation energy is less significant for the plans and energy ranges considered.

DISCUSSION

While many tumours can be effectively treated with radiation therapy as presently practised, there remain many areas of the body where the achievement of tumouricidal dose levels is difficult, if not impossible, because of limitations in the tolerance of normal tissues. This is particularly true of tumours lying within the abdominal cavity or retroperitoneal area where the tolerance of normal bowel and kidney limits the dose that can be delivered to the region.

With the advent of newer diagnostic techniques which permit more precise localizations of tumours, including irregular three-dimensional volumes, it becomes feasible to consider methods for delivering a tumouricidal radiation dose to these defined volumes while greatly limiting the dose to the surrounding tissue. The proposed method of plan selection postulates that the probability of radiation-induced complications is related to the volume of normal tissue irradiated to a high dose. This is then used as a basis for selection of the "best" treatment plan as the one with the smallest complication probability factor.

The analysis of external beam treatment of the pelvis for carcinoma of the cervix illustrates the relative simplicity of this technique. Marked CPF differences occur with the three selected treatment techniques; however, less variation is observed with beam energy. This analysis suggests that complex radiation delivery plans may offer a substantial improvement in dose distributions, while higher beam energies are relatively less advantageous. We realize that the evidence for a linear relationship between irradiated volume and complication probability is inferential; it may have to be modified as more information becomes available. The method described is a general technique for quantitatively relating volume in irradiated tissue. It allows more precise evaluation of treatment plans and when correlated with clinical outcomes should permit more exact definition of the functional relationship between volume irradiated, dose delivered, and risk of complications. We realize that a weighted dose-volume is probably not the only variable of importance in determining the complication risk and suggest using this as a starting point for identifying other clinically relevant parameters.

The proposed method of analysis offers an index for comparison of treatment plans that is simple in application and readily adaptable by most centres. The basis for analysis offers a broad application in comparing various conventional treatment plans.

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Book reviews

Technology and interpretation of nuclear medicine procedures. By D. Bruce Sodee and Paul J. Early, pp. 520, 831 illus., 2nd edn., 1975 (Henry Kimpton Publishers, London), £14·60.

This is the second edition of a volume designed to be used in conjunction with another, entitled *Textbook of Nuclear Medicine Technology*. While the latter provides relevant background reading and additional information, this volume is intended to guide and complement practical work during training, and can well be used on its own. Together the textbooks provide an introduction to the background and practice of Nuclear Medicine for either clinical or technical practitioners. Both volumes are divided into two parts dealing with (so called) "Nuclear Science" and "Clinical Nuclear Medicine".

The "Nuclear Science" section of this volume is based on teaching exercises developed over many years at the Nuclear Medicine Institute, Cleveland, Ohio and used in the training of technologists. It is written as a laboratory manual. Brief statements of the purpose of each particular exercise are followed, often on a split page, by sections on the apparatus and materials required, step-by-step instructions, data treatment and problems; helpful remarks are confined to the other half of the page. This allows the teaching points to be emphasised, while maintaining the clarity of practical procedures. Exercises cover the fundamentals of instrumentation, radiochemistry and health physics. As examples, detailed prescriptions are provided for the setting up of a scintillation counter, checking the performance of a gamma camera, preparing doses, decontamination and procedures at the patient's bedside. Notably absent is practice with liquid scintillation counting.

The "Clinical Nuclear Medicine" section is intended to provide guidelines for the technical application and the interpretation of current routine procedures. It is directed additionally at the clinician in training. Often again employing the split-page technique, a wide range of tests are described such as, for example, *in vitro* thyroid tests, absorption and clearance studies, radioimmunassay, dynamic and static organ imaging. Clinical indications for the tests are given, and in addition detailed procedures, including where necessary preparation of the radiopharmaceuticals, together with illustrations and possible interpretations of the results.

While many centres will have established different protocols, fashions change and interpretations alter with increasing experience; it is still useful to have accounts of sufficiently detailed methods for comparison. This carefully edited and well illustrated volume can be highly recommended as a reference for those starting their careers in the field. It may even be useful to those established practitioners with less expertise than is brought together here.

M. F. Cottrall.

Clinical Radiobiology. By W. Duncan and A. H. W. Nias, pp. 221, 1977 (Edinburgh; Churchill Livingstone), £9·50.

This 220-page hard backed book is written expressly to cover the syllabus of the Part 1 F.R.C.R. examination in radiobiology. It is thus directed towards the young radiotherapist and, as such, is pitched at a practical clinical level. The fifteen chapters cover the standard radiobiological approaches to the cell cycle, survival curves, recovery from radiation damage and the early and late effects of irradiation. References are appended to each chapter and a list of suggestions for further reading.

The most impressive aspect of this book is how closely the authors stick to their brief. Although the reader is given a broad background to each subject, no more than the standard teaching is included and Professor Duncan and Dr. Nias avoid the pitfall of expounding in great detail recent advances or controversial issues. The format of the book is extremely pleasing. The type face is clear and subheadings break up chapters. The clear line drawings are excellent although they can never replace for the radiotherapist the familiarity of a clinical illustration or X ray.

Although I am not quite sure of the relevance of radiobiology to the modern radiotherapist, it seems proper that he should be able to attempt an explanation for his clinical findings on a basis of cell kinetics.

Although it has competitors, this book deserves a place as one of the standard text books for the F.R.C.R. I find the exclusion of cytotoxic chemotherapy and its interaction with radiotherapy on normal tumour cell kinetics disappointing. If radiobiology is to have continued clinical impact, it must become less compartmentalized and become less of a subject and more of an approach. The opportunity to include a chapter on statistics may also have helped the radiotherapist.

Margaret E. Spittle.

1978, *British Journal of Radiology*, *51*, 375–380 MAY 1978

On the nature and significance of the radiation outside the beam in neutron therapy

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ABSTRACT

Measurements have been made of beam profiles at 10 cm deep for the neutron beam of mean energy 7.5 MeV produced by the MRC cyclotron at Hammersmith Hospital. Neutron and γ-ray doses in water were measured with a tissue-equivalent chamber and a Geiger-Müller counter. Far outside the beam the radiation consists mostly of γ rays penetrating the shielding. Perfect shielding would reduce this but the profile of biologically effective dose would still be worse than that from conventional X- and γ-ray generators owing to the high RBE of small doses of neutrons. The main hazard to the patient is probably that of carcinogenesis. An approximate assessment is made of this hazard which is compared with that estimated in previous publications.

Shielding and collimation of neutron generators is more difficult than is the case with X- or γ-ray machines. The conventional criterion used in the design of the latter is that the radiation penetrating the shielding should not exceed 0.1% of the intensity in the useful beam; for practical reasons it has been necessary to accept higher levels for neutron generators. The purpose of the present paper is to characterize the radiation absorbed by regions of the patient outside the therapeutic beam during neutron treatment at Hammersmith Hospital, to assess whether this radiation could be sensibly reduced, and to estimate the hazard associated with it.

MEASUREMENT OF THE STRAY RADIATION AND ASSESSMENT FOR PERFECT SHIELDING

As a guide to the dose-distribution at a depth in the patient we have made measurements of beam profiles at a depth of 10 cm in a water phantom. We made these measurements with two field sizes (9.5×9.5 cm and 21×21 cm) and with the diaphragms closed. By subtracting the latter, the component of the radiation due to scattering within the irradiated volume can be estimated; this would be unaffected by any improvement in shielding and represents the minimum quantity of stray radiation which would occur if the shielding were perfect. The water phantom was a tank 30 cm thick with its front surface at the normal position of the patient's skin during neutron therapy, namely 120 cm from the target. Details of the set-up and monitoring have been given by Bewley and Parnell (1969).

The total dose ($D_n + D_\gamma$) was measured with a 1 cm³ tissue-equivalent (TE) chamber filled with TE gas, using both polarities. The difference between readings with different polarities was small on the axis but rose to 30% at 60 cm away. The dose due to γ rays, D_γ, was measured with an energy-compensated Geiger-Müller counter (Type MX 163) surrounded by at least 1 mm of ^{6}Li metal. The neutron sensitivity of the counter was assumed to be zero. The partial dose of neutrons, D_n, was obtained by subtraction. Some indication of neutron spectrum was obtained by exposing various activation and fission detectors.

The profiles could be presented in various ways. In Figs. 1 and 2 they are normalized to $D_n = 100\%$ at 10 cm deep on the beam axis. This form of presentation shows at once the dose off the axis for a given dose delivered to a model tumour at 10 cm deep. The measured profiles of D_n and D_γ are given in Fig. 1, together with profiles measured with the diaphragms closed (a solid wooden plug was inserted in place of the usual collimator). In this case the profile is shown as a percent of the central neutron dose at 10 cm deep with the 9.5×9.5 cm field. The diagram

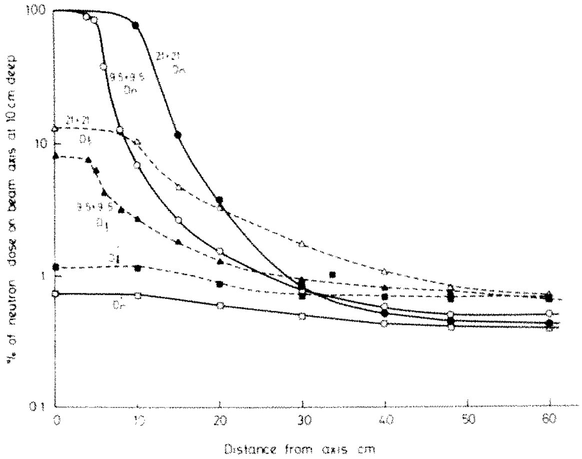

FIG. 1.

Profiles of neutron- and γ-ray dose (D_n and D_γ) at 10 cm deep to a 9.5×9.5 cm and a 21×21 cm field and with the diaphragms closed (D_n' and D_γ'). The neutron dose on the beam axis is normalized to 100%; the doses with the closed diaphragms are normalized to 100% neutron dose for the 9.5×9.5 cm field.

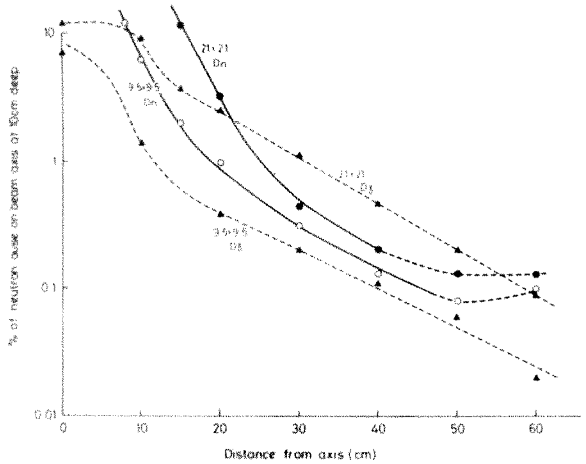

FIG. 2.

* Profiles of neutron- and γ-ray dose for perfect shielding, obtained from the data in Fig. 1.

shows that at large distances from the axis D_γ exceeds D_n and that the radiation at these distances, both neutron and γ, is mostly due to penetration of the shielding. The reason why the curves for the two field sizes cross is that each is referred to $D_n = 100\%$ on the axis, the percentage depth dose and backscatter factors for the two fields being different. The curves would not cross if both were referred to a given neutron output from the target.

Figure 2 shows the effect of subtracting the radiation with the diaphragms closed. At large distances from the axis the values of D_n are uncertain because they were derived by a triple subtraction. First, for each field size D_γ was subtracted from $(D_n + D_\gamma)$ and the same was done for the closed diaphragms. Then D_n for the closed diaphragms (D_n' in Fig. 1) was subtracted from D_n for each field. In each case the residue was less than half the sum. Only one subtraction (the last) was needed for D_γ. After a fairly sharp initial fall, D_γ can be seen to decrease exponentially. D_n seems to be decreasing less rapidly at large distances but the points at 50 and 60 cm are very uncertain as noted above. At large distances from the beam edge D_γ exceeds D_n for the 21 × 21 cm field but not for the 9.5 × 9.5 cm field. The reduction in stray radiation given by perfect shielding would be considerable at large distances from the beam axis: for example, at 50 cm from the axis of the 9.5 × 9.5 cm field the measured percentage values of D_n and D_γ were 0.5 and 0.7 respectively, compared with 0.08 and 0.06 for perfect shielding.

Figure 3 shows the profiles for the 9.5 × 9.5 cm field measured with various activation and fission detectors. As the threshold energy of the detector rises the profile becomes sharper, showing that the mean neutron energy outside the beam is considerably lower than inside. An Np fission counter (effective threshold about 0.3 MeV) gave a profile very close to that of the reaction $^{115}In(n,n')^{115}In^m$. A practical consequence is that In and Np are good detectors for estimating relative neutron doses received by patients during neutron therapy.

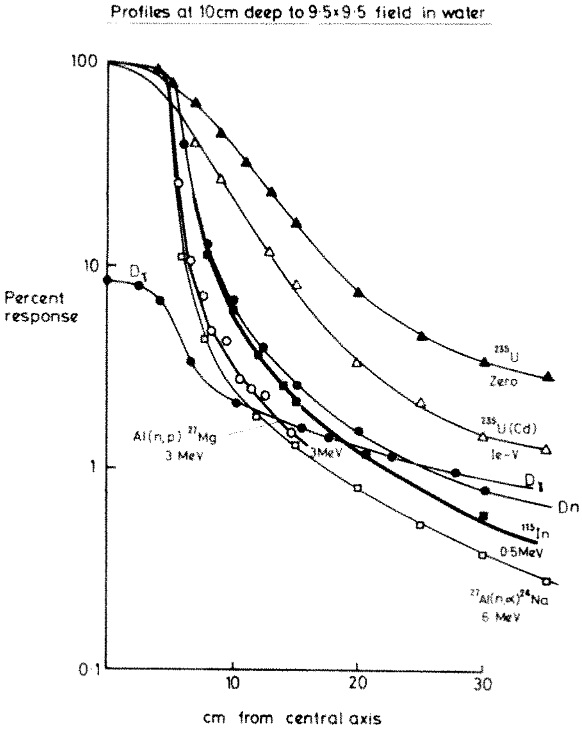

FIG. 3.

Profiles at 10 cm deep to a 9.5 × 9.5 cm field measured with various activation and fission detectors. The approximate threshold energies of the detectors are given alongside the curves.

Biologically effective profile

To estimate the biological effect of this stray radiation one needs some method of combining the neutron- and γ-ray components. The RBE of neutrons relative to γ radiation depends on the biological end-point chosen, the neutron energy and the dose per fraction delivered. The most accurate and comprehensive information we have is for skin where RBE values have been measured over a range of neutron doses from more than 1000 rad down to 70 rad. When extrapolated to lower doses this line agrees reasonably with estimates of RBE for carcinogenesis and life-shortening in mammals (Fig. 5 and discussion in next section). We have therefore used it

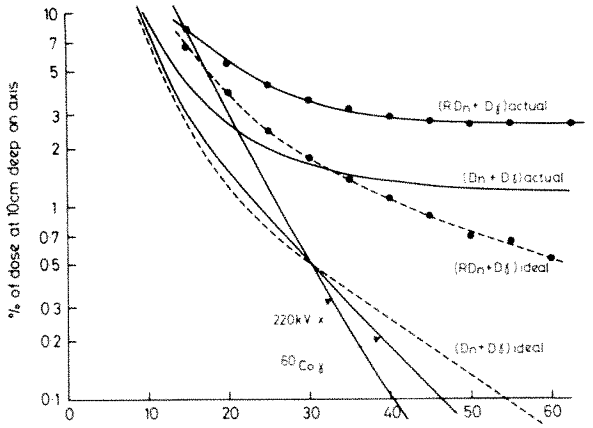

Fig. 4.

Profiles of total dose (D_n+D_γ) and "effective" dose (RD_n+D_γ) at 10 cm deep to a 9.5 × 9.5 cm field. R is taken from the line in Fig. 5. Measured profiles for 220 kV X rays and ^{60}Co γ rays are included for comparison.

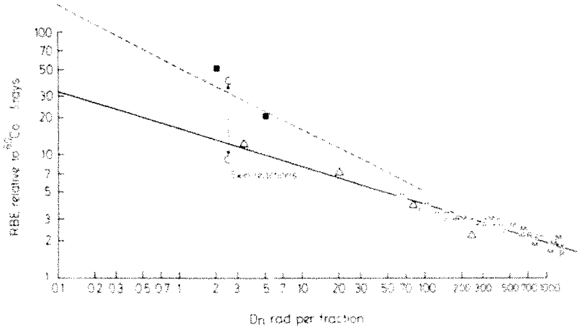

Fig. 5.

RBE of fast neutrons for carcinogenesis and skin reactions. The line for skin reactions refers to measurements made with the neutron beam at Hammersmith on mice (M), rats (R), pigs (P) and humans (H). The points ■ are for induction of mouse mammary carcinomas in rats with fission neutrons (Vogel and Zaldivar, 1972; Vogel, 1974). The dotted line above 10 rad is for leukaemogenesis in survivors of the bombs at Hiroshima and Nagasaki (Rossi and Kellerer, 1974) and below 10 rad for induction of mammary carcinomas in mice (Shellabarger *et al.*, 1974). △—Non-specific life-shortening in mice after irradiation with γ rays or fission neutrons, mean of both sexes (Ainsworth *et al.*, 1976). ⊂ Range of values for induction of mammary carcinoma in mice with cyclotron neutrons at Hammersmith Hospital.

as a guide for combining the neutron- and γ-ray components. The standard neutron tumour-dose per fraction during the radiotherapy is 130 rad so we have used this to set the RBE for the 100% point on the axis.

Figure 4 shows the profiles of "effective dose" (RD_n+D_γ) where R is the RBE, estimated in this way for the 9.5 × 9.5 cm field, together with other information for comparison. Outside the beam the mean neutron energy is lower, as indicated by Fig. 3, so the RBE of the neutron component outside the beam is likely to be greater than that of the neutrons in the beam. No allowance has been made for this in Fig. 4. The profiles for 220 kV X rays and ^{60}Co γ rays were measured with similar field sizes and are reproduced from Bewley and Parnell (1969). Note however that the 100% value is now at 10 cm deep instead of on the surface. The ideal profile of total dose, (D_n+D_γ), is not very different from that of the ^{60}Co γ rays, showing that equivalent profiles of absorbed dose are possible with adequate shielding. The actual profile of total absorbed dose does not, however, fall below 1%. When the RBE factor is applied, the profiles of "effective dose" lie considerably higher, the actual "effective dose" never falling below 2.5%. The levels of stray radiation are considerably higher than those shown in Figs. 4 and 5 of Bewley and Parnell (1969). This is partly because of the shift of the 100% point noted above (a factor of about two), partly to the fact that the techniques used previously were insensitive to low energy neutrons, and partly to the use of RBE values much greater than the value of three used previously. For example, at 60 cm from the axis D_n is 0.5% and the assumed value of RBE is 18.

Estimation of Hazard

The principal hazard to the patient arising from stray radiation is probably carcinogenesis. There has been no indication that patients have suffered any untoward depression of haemopoiesis. The RBE of neutrons for killing of bone-marrow cells is lower than that for other end-points *in vivo*; the profiles of "effective dose" in Fig. 4 are therefore likely to be overestimates for immediate effects on the bone marrow. The RBE of neutrons for killing and transformation of circulating lymphocytes has also been found to be low, in the range 1–2.5 (Hedges and Hornsey, 1978).

Data of the RBE of neutrons for carcinogenesis are scanty. Many reported experiments did not include sufficient variation in the dose levels of neutrons and γ rays for a satisfactory estimate of RBE to be made. Others used doses that were too big for the present purpose. Figure 5 summarizes what little could be found. The points ⊂ represent a range of preliminary values of RBE of the Hammersmith neutron beam for reduction in latent period before the appearance of mammary neoplasms in C$_3$H mice carrying the milk factor. Experiments are currently in progress to extend these observations to lower dose levels; the work will be fully reported later (Hornsey, to be published). Most of the RBE values for carcinogenesis lie within a factor of two of the extrapolated line describing RBE values for acute skin reactions. The experimental results were obtained with lower energy neutrons for which the RBE might be expected to be somewhat larger. The neutrons outside the therapeutic beam are also of lower energy than those within the beam. For calculating the carcinogenic effect of these neutrons we have used twice the RBE obtained by extrapolating the line for acute skin reactions. This is clearly a gross simplification. It ignores variations of RBE for induction of different types of tumour and the effects of fractionation (Fry, 1976), but we believe that the resulting values of RBE are not likely to be much too small.

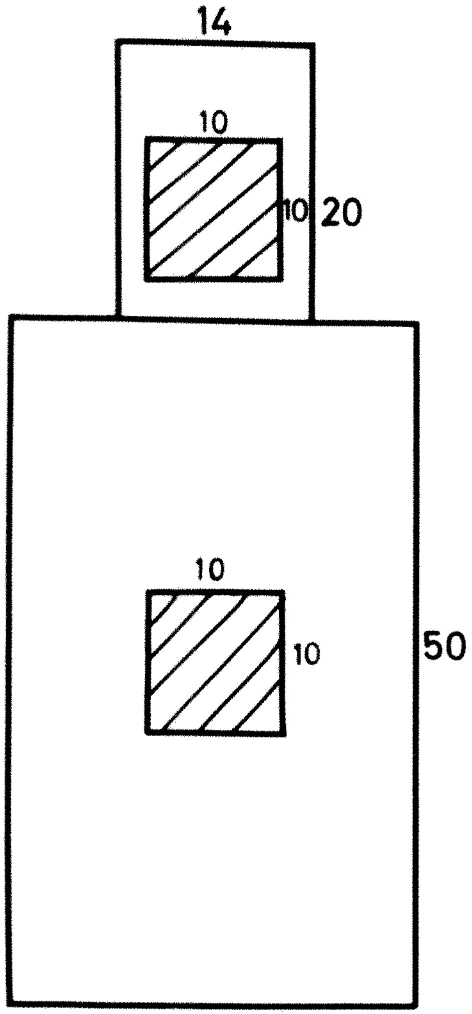

Fig. 6.

Model of the human body for calculation of the carcinogenic risk. The model is 20 cm thick, arms and legs are excluded. Two alternative positions of an applied field are shown.

In estimating the hazard attached to these "effective doses" we need a relationship between dose of photons and incidence of carcinogenesis. It is conventional to assume a linear relationship at low doses. However, if RBE varies with dose in the way indicated by Fig. 5, the incidence of carcinogenesis cannot be linear for both types of radiation. For neutrons the incidence would have to vary with a fractional power of the dose. The problem of dose effect relationships for carcinogenesis is an extremely complicated one (Fry, 1976; Brown, 1976); for the present purposes a linear relationship for photons must suffice. At higher doses the incidence of carcinogenesis is generally found to reach a plateau and then decline.

A recent analysis by Smith and Doll (1976) of the incidence of malignant disease in women treated by radiotherapy for uterine bleeding is perhaps the most relevant for the present purpose. They found no increased incidence for the first five years after treatment. At later times they estimated the risk of leukaemia at 1.1 per 10^6 women-year-rad, with an additional risk four times as great from other malignancies. Accordingly we have calculated the risk per patient per year, H, as

$$H=\frac{5.5\times 10^{-6}}{V}\int (RD_{\mathrm{n}}+D_{\gamma})\,\mathrm{d}V,$$

V being the volume of the patient.

In performing this integration we have used a simplified model of a patient, as shown in Fig. 6, with a 10×10 cm field applied to the face or the trunk. The model has no arms or legs because few malignancies arise in the limbs. The trunk, head and neck were taken as 20 cm thick. The dose at the centre of the field, at 10 cm deep, was taken as 1560 rad n+125 rad γ, given in 12 equal fractions. The profiles of Figs. 1–4 were assumed to represent average values

TABLE I

Estimate of risk of new malignancy resulting from a full course of neutron therapy. Unit is risk per year $\times 10^{-3}$, after the first five years.

Position of field	Beam	
	Actual	Ideal
Head	4.1	3.1
Trunk	5.4	4.6

at all depths. The RBE values of Fig. 5 were multiplied by two to allow for a possible underestimate of RBE of the relatively lower energy neutrons outside the main beam. The volume inside the 10 × 10 cm field was not included in the calculation because new primaries seldom develop in the volume given a curative dose of radiotherapy, corresponding to the reduced incidence of carcinogenesis with high doses noted above. The result of this calculation is given in Table I.

Discussion and Conclusion

The measured profiles (Fig. 1) show that far outside the beam more than half of the dose due to stray radiation arises from γ rays. Thus, at 50 cm from the axis of the 9.5 × 9.5 cm field, $D_\gamma = 0.007$, $D_n = 0.005$, $(D_n + D_\gamma) = 0.012$ relative to the neutron dose on the axis. With the 21 × 21 cm field D_γ is about twice D_n. Measurement of total dose alone, $(D_n + D_\gamma)$, would seriously overestimate the importance of the stray radiation.

Far outside the beam most of the radiation is due to penetration of the shielding rather than scattering. The neutron doses arising from the two mechansisms are equal at 20–25 cm from the beam edge. With perfect shielding the reduction in dose orthogonally to the beam axis would become approximately exponential at some distance outside the beam edge (Fig. 2), but estimation of neutron dose far from the beam is uncertain owing to the triple subtraction required. Perfect shielding would reduce the radiation levels by factors of more than five beyond 60 cm from the beam axis.

The neutron component outside the beam has a lower mean energy than inside the field (Fig. 3). When activation or fission detectors are used to estimate the neutron dose care must be taken to choose a detector whose response-function is a reasonable match to the tissue kerma as a function of neutron energy.

With perfect shielding the total dose $(D_n + D_\gamma)$ would decrease in a manner comparable to the stray radiation from a ^{60}Co therapy machine (Fig. 5). But when allowance is made for the RBE of the neutron component and for the fact that RBE usually rises as the dose falls, the effective level of stray radiation would greatly exceed that of the radiation from a ^{60}Co machine. When the RBE relation of Fig. 5 is used, the effective dose with perfect shielding would exceed that from ^{60}Co by a factor of ten at 50 cm from the beam axis. The effective dose with the shielding actually used is larger again by a factor of four.

The RBE of fast neutrons depends on the biological material, the end-point under consideration and the dose and energy of the neutrons. The RBE for haemopoietic cells is relatively low and depression of the haemopoietic system has not been a problem in our use of neutron therapy. The main hazard to the patient arising from stray radiation is probably the risk of inducing a new malignancy. The biggest single uncertainty in estimating this hazard lies in the appropriate value of RBE to be used. There is considerable evidence that RBE for carcinogenesis may be large at low doses, in the range 10–100; the extrapolated relation between dose per fraction and RBE for acute skin reactions seems to give a reasonable estimate.

The analysis of Smith and Doll (1976) was used to estimate the risk when the neutron doses had been converted to effective doses of X or γ rays. Their estimate of 5.5×10^{-6} per rad per patient-year is not dissimilar from that of the BEIR committee based on the populations of Hiroshima and Nagasaki (National Academy of Science, 1972). Our estimates of the risk to the patient is 3 to 6×10^{-3} per patient-year after the first five years. If neutron therapy offers a substantially better chance of controlling the disease than other methods of treatment this does not seem an excessive price to pay, particularly in older patients. The uncertainty in the estimate is big, perhaps as large as a factor of ten either way. It arises mainly from lack of knowedge of the carcinogenic effect of small fractionated doses of neutrons. Uncertainties in the measurement of dose-distributions are smaller. Use of perfect shielding would reduce the risk by only 25%. This is because improved shielding would exert its greatest effect far from the beam where the dose is small anyway; the main contribution to the risk as calculated by the method used here is the volume outside but close to the edge of the beam. This is also the reason why the fields on the head and trunk carry similar risks. Inclusion of the volume within the beam would increase the estimate of risk by 50%.

Previous estimates of the hazard to the patient from stray radiation during neutron therapy have been made by Parnell and Kelsey (1972) and Geraci *et al.* (1975). These were based on more limited data, particularly with regard to division of the stray radiation into its component parts of neutrons and γ rays. For a survival time of 30 years after treatment the estimates of risk are: Parnell and Kelsey 0.03 (RBE = 16), Geraci *et al.* 0.18 (RBE = 36), this work 0.12. All estimates of this kind should however be regarded as extremely dubious. The risk of carcinogenesis following irradiation depends on many factors in addition to the radiation dose, for example the age of the patient at exposure (Smith and Doll 1976, Table VII). Also patients with cancer may be more liable to develop a second primary regardless of the treatment given to the first.

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Book reviews

Medical radiation exposure of pregnant and potentially pregnant women. NCRP Report No. 54 pp. 27, 1977. (NCRP Publications, Washington), $4.00.

This is a valuable report, and each X-ray department (or at least each RPA and RSO) should have one and use it. The hazards are surveyed as quantitatively as may be in the circumstances, and also the factors on which postponement of a radiological examination, or an abortion, would have to be based. It is emphasised that in the one or two weeks after conception the hazard to be considered is that of undetectable spontaneous abortion, which is of much less importance than the malformations that could result from irradiation during major organogenesis.

The general conclusion is that the number of examinations which could be postponed without detriment to the medical care of the woman and/or any unborn child, and which also involve high enough doses to give cause for concern, is so small that although what we call the "ten-day rule" must always be borne in mind, it results in little reorganisation in practice.

One useful feature is Appendix A, containing data to enable the dose to an embryo-fetus from a radiographic examination to be estimated. There should, however, have been an indication of the very approximate nature of any dose estimates not based on measurements on the X-ray tube concerned. In addition, the English could have been improved in such sentences as "The time . . . may also be relatively insensitive" (p.6).

S. B. Osborn.

The Adult Postoperative Chest. By Myron Melamed, Florencio A. Hipona, Carlos J. Reynes, Walter L. Barker, and Santiago Paredes, pp. xviii+578, 1977 (Charles C. Thomas, Springfield, Ill., USA), $31.50.

To the average diagnostic radiologist the reporting of a post-operative chest X ray is a singularly unrewarding task for, without a detailed knowledge of the operative procedure, radiological interpretation is fraught with hazard and the report is of little value to the thoracic surgeon. Apathy is thus nurtured by ignorance and furthers a lack of interest on both sides.

This ambitious book attempts to deal with such enforced lack of knowledge by a cohesive approach aimed to dovetail surgical manoeuvre into radiological interpretation. The four radiological authors are joined by a fifth who is a practising thoracic surgeon and the text is therefore authoritative and the conclusions practical. The many illustrations are well chosen and make their point although reproduction is not of the highest quality.

The book covers the post-operative appearances following both cardiac and pulmonary surgery but, as the title indicates, operations on children are not included; the scope is limited and the value as a comprehensive work is materially curtailed. As far as it goes this is a good book and should be kept in all X-ray Departments in those hospitals where thoracic surgery is carried out. There is a need for a companion volume (albeit smaller) to cover the appearances of the post operative chest in children.

Basil Strickland.

1978, *British Journal of Radiology*, *51*, 381–386 MAY 1978

The radiosensitizing effect of metronidazole and misonidazole (Ro-07-0582) on a human malignant melanoma grown in the athymic mutant nude mouse

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(*Received July, 1977 and in revised form October, 1977*).

ABSTRACT

The radiosensitizing effect of two electron-affinic nitroimidazoles, metronidazole and misonidazole (Ro–07–0582), has been tested on a human malignant melanoma grown subcutaneously in the athymic mutant nude mouse. A ^{60}Co therapy unit was used for local irradiation of the mice. Metronidazole in doses of 750 mg/kg and misonidazole in doses of 500 mg/kg were administered intraperitoneally to the animals 45 min before exposure to 1250 rad. The time necessary for the tumours to regrow to their original sizes was compared with that of tumours treated with 1250, 1875 and 2500 rad without drug. The enhancement ratios were found to be 1.2–1.3 and 1.4–1.5 for metronidazole and misonidazole respectively. It is concluded that misonidazole is a more efficient hypoxic cell radiosensitizer for this human malignant melanoma than metronidazole. The former may prove to be of value in human radiotherapy.

As early as 1955 it was postulated that the presence of small proportions of radioresistant hypoxic cells in tumours could limit the success of radiotherapy in some clinical situations (Thomlinson and Gray, 1955). Since that time, radiotherapists have tried to solve this problem by administration of hyperbaric oxygen during irradiation, by use of densely ionizing radiation and by development of different irradiation regimes to optimize the effect of reoxygenation. Some therapeutic improvements have been obtained, but none of the techniques mentioned above have eliminated the clinical problem that the radioresistance of hypoxic tumour cells represents (Adams *et al.*, 1976).

Recently, several electron-affinic chemical compounds have been shown to be efficient radiosensitizers for hypoxic mammalian cells irradiated *in vitro* (Chapman *et al.*, 1972; Chapman *et al.*, 1973; Adams *et al.*, 1971; Asquith *et al.*, 1974.). These sensitizers resemble oxygen in their mode of action and are not active against well-oxygenated cells (Asquith *et al.*, 1974). Unfortunately, most of these compounds failed to enhance the radiosensitivity of hypoxic cells *in vivo*. The drugs were either too toxic at the concentrations necessary for radiosensitization, too highly attached to serum proteins or too rapidly metabolized (Fowler *et al.*, 1976a). However, two compounds, the 5-nitroimidazole metronidazole, and the 2-nitroimidazole misonidazole (Ro-07-0582), have toxicological and pharmacological properties in man making them promising as clinically useful hypoxic cell radiosensitizers (Foster *et al.*, 1975; Gray *et al.*, 1976; Dische *et al.*, 1976; Urtasun *et al.*, 1977). The radiosensitizing effect of these two compounds has been tested *in vivo* on various murine solid tumours and normal tissues. For single exposures to X rays after administration of the drugs in doses likely to be tolerated in man, enhancement ratios up to 1.3 have been reported for metronidazole (Stone and Withers, 1974; Rauth and Kaufman, 1975), while misonidazole exhibited enhancement ratios ranging from 1.1 to 1.6 (Denekamp *et al.*, 1974).

The intention of the present work is to investigate the radiosensitizing effect of metronidazole and misonidazole on a human tumour. For this purpose the mutant nude mouse was used as host for a human malignant melanoma.

MATERIALS AND METHODS

Animals

The mutant nude mouse (Isaacson and Cattanach, 1962; Flanagan, 1966; Rygaard, 1973) accepts transplanted human neoplastic tissue because of recessive thymic aplasia. Several investigations have indicated that the response to therapy of human tumours grown in this laboratory animal resembles that seen in clinical studies of patients (Povlsen and Rygaard, 1974; Povlsen and Krag Jacobsen, 1975; Brustad *et al.*, 1976; Rofstad *et al.*, 1977).

Young male nu/nu/BALB/c/BOM mice were used for the experiments described here. The mice were kept in a special room at 27°C with automatically regulated 12 hour light and dark periods, under conventional but strict conditions.

Tumour material

The malignant melanoma (E.E. malignant melanoma) chosen for this investigation was taken from a lymph node metastasis in the left axilla of a 62-year-old man. Histologically, the tumour tissue was composed of melanin-poor atypical nevus-cells. Both cells and nuclei showed a great variation in size and shape. Numerous mitoses were seen.

Radiosensitizers

Metronidazole (2-methyl-5-nitroimidazole-1-ethanol) was supplied by Poulenc Ltd., Montreal, Canada, while misonidazole (1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanol) was obtained as a gift from Roche Products Ltd., Hertfordshire, England.

Inoculation, growth and measurement of tumour size

Immediately after surgery, the tumour tissue was cut into representative cubes approximately 2×2×2 mm in size and inoculated subcutaneously on the dorsal surface of the animals. One week after the inoculation, the transplants started to grow and the mice developed non-invasive tumours histologically indistinguishable from the original tumour material. The tumours consisted of a large central necrosis surrounded by an outer shell of vital, proliferating cells. The cells lying closest to the necrotic areas are probably poorly oxygenated and thus radioresistant.

Two axes of the tumours were measured with calibrated calipers, and the cross-sectional area of the tumours, calculated as being elliptical, was used as parameter for the tumour size. At the day of irradiation the cross-sectional areas ranged from 50 to 100 mm^2. Passage seven of the malignant melanoma was used for the experiments described here.

Dosimetry and irradiation procedure

The irradiation procedure was described in detail in a previous article (Rofstad *et al.*, 1977). Only a short description is given here. The animals were irradiated locally without anaesthesia at a source-skin distance of 80 cm by applying one tangential radiation field from a 5000 Ci ^{60}Co therapy unit (TEM, Mobaltron 80). Acceptable dosimetric conditions were obtained by partly immersing the mouse, placed in a mouseholder, in a water phantom, whereby the entire tumour was positioned under water and at a distance from the outer surface of the phantom wall greater than that corresponding to the ionization maximum of the radiation used. Measurements made with thermoluminescence discs (TLD 100 LiF ribbon, Harshaw) placed at the ionization maximum varied within a few percent of the corresponding ionization chamber readings of 90 rad/min. The variation of dose within each tumour was determined to be less than 10%.

Measurement of radiosensitizer concentrations in serum

The radiosensitizers were dissolved in physiological saline and administered intraperitoneally to the animals. Blood was collected from the mice in heparinized tubes by heart puncture. A spectrophotometric assay similar to that developed for metronidazole (Urtasun *et al.*, 1974) was applied for both metronidazole and misonidazole. 2.7 ml ethanol was added to 0.3 ml whole blood. The mixtures were allowed to stand for 10 min and were then centrifuged at 2500 g for another 10 min. The optical density of the supernatant was measured at 314 and 318 nm for metronidazole and misonidazole respectively.

Experiments

Preliminary clinical trials have indicated that quantities of metronidazole from 50 to 100% higher than that of misonidazole will cause the same level of toxicity in patients (Fowler *et al.*, 1976a). To make the studies of the two radiosensitizers comparable, animals treated with metronidazole were given 750 mg/kg bodyweight while those treated with misonidazole were given 500 mg/kg bodyweight, corresponding to peak serum concentrations of approximately 500–600 μg/ml and 400–500 μg/ml (Fig. 1).

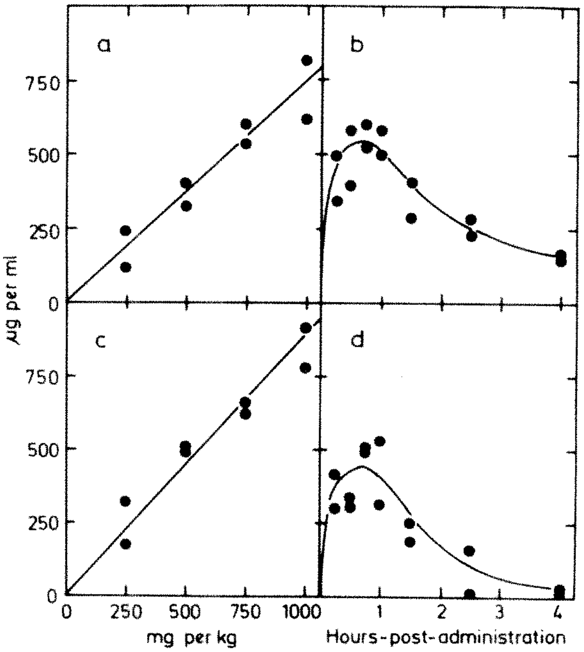

Fig. 1.

Serum concentration in the mutant nude mouse of (a) metronidazole as a function of the amount of sensitizer injected i.p. measured 45 min. after injection, (b) metronidazole as a function of the time after injection of 750 mg/kg i.p., (c) misonidazole as a function of the amount of sensitizer injected i.p. measured 45 min. after injection and (d) misonidazole as a function of the time after injection of 500 mg/kg i.p.

From Fig. 1 it also appears that the peak serum concentration of the two radiosensitizers is reached 30–60 min. after the injection. It has been reported that the concentration of metronidazole in the centre of solid tumours reaches that in blood with a lag-time of approximately 15 min. (Urtasun *et al.*, 1974). To ensure a high concentration of the radiosensitizers in the tumours during irradiation, it was decided to start the irradiation 45 min. after administration of the drugs.

The effect of the sensitizers were tested for an acute radiation dose of 1250 rad. This dose was chosen because it was expected to be large enough to inactivate a large proportion of the well-oxygenated tumour cells and small enough not to inactivate the whole tumour even if the radiosensitizers exhibited extremely high enhancement ratios.

The available animals were divided into the following groups:

(a) One group receiving 750 mg/kg bodyweight of metronidazole 45 min before irradiation with 1250 rad.

(b) One group receiving 500 mg/kg bodyweight of misonidazole 45 min before irradiation with 1250 rad.

(c) Four reference groups, one remaining unirradiated, one receiving 1250 rad alone, one receiving 1875 rad alone and one receiving 2500 rad alone.

RESULTS

Figure 2 shows the change in tumour size for all six groups of animals as a function of the time after irradiation. Within each group of animals, the response to treatment appeared independent of the initial cross-sectional area of the tumours which ranged from 50 to 100 mm². The areas at the day of treatment were therefore normalized to unity. From Fig. 2 it can be seen:

(1) For tumours treated with radiation alone, the post treatment delay (*i.e.* the time from the day of treatment to the day the tumours have regrown to their original sizes) increases approximately linearly with increasing dose (cf. also Fig. 3a).

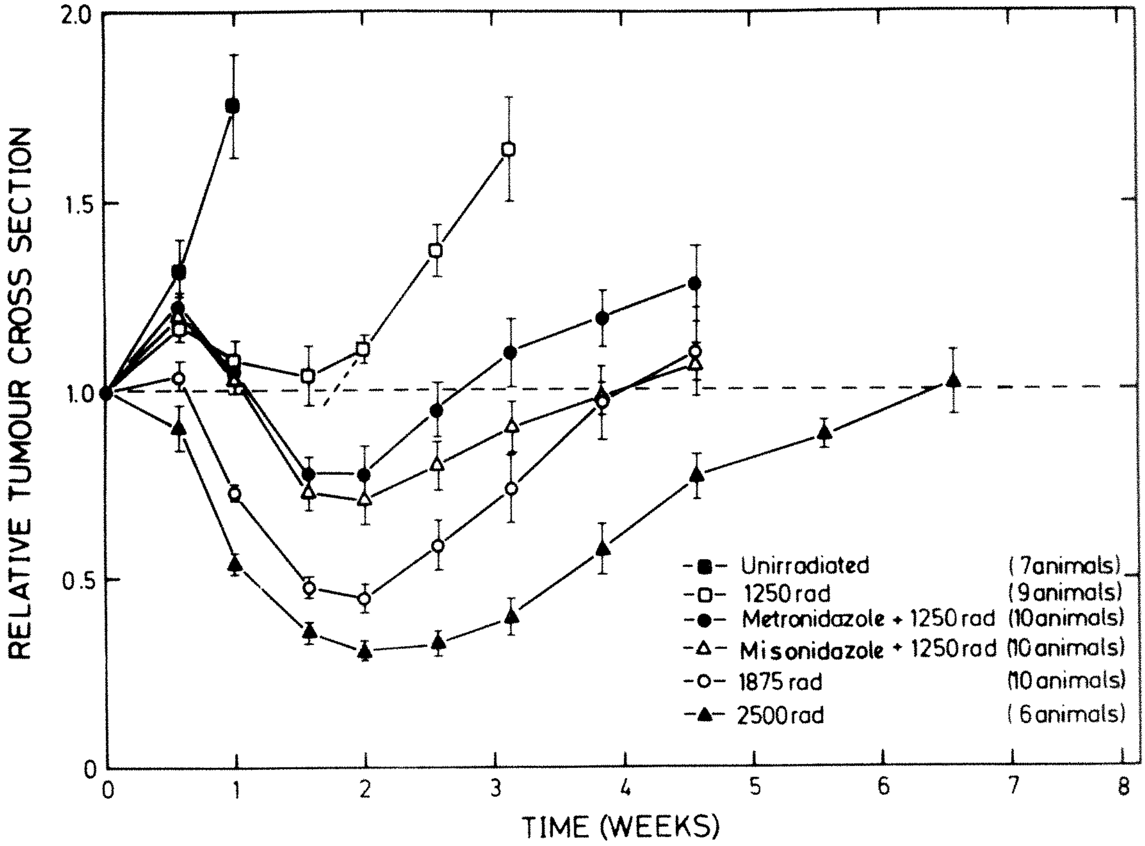

FIG. 2.

Changes in tumour cross sectional area relative to that at the time of irradiation of a human malignant melanoma grown subcutaneously in the mutant nude mouse. The vertical bars indicate the standard deviation of the mean.

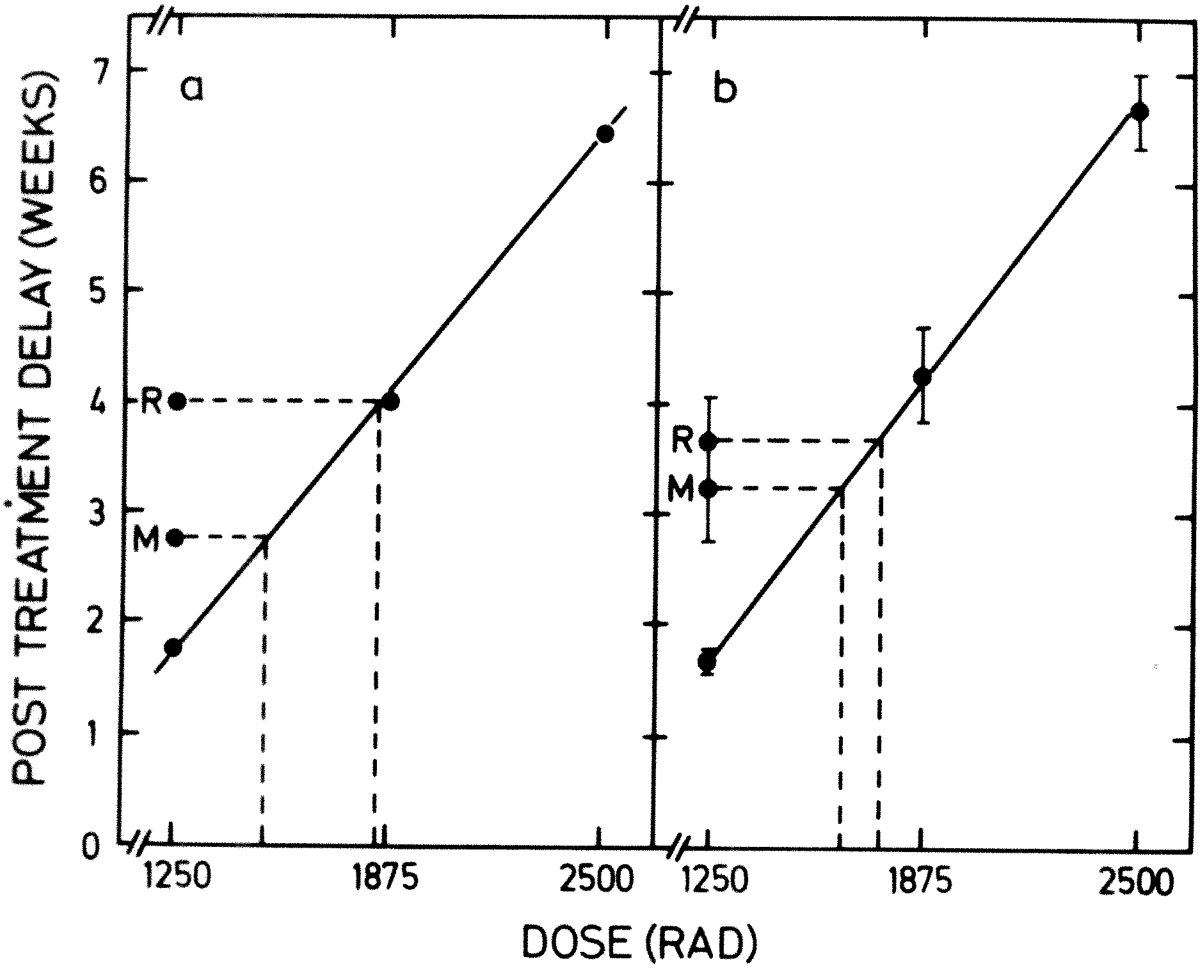

FIG. 3.

(a) Post treatment delay of the mean tumour size plotted versus dose for a human malignant melanoma grown in the mutant nude mouse. (b) Mean post treatment delay plotted versus dose for the same experiment as in (a). The vertical bars in (b) indicate the standard deviation of the mean. The symbols M and R are used to indicate the points showing the effect of the sensitizers metronidazole and misonidazole (Ro–07–0582) in combination with radiation. The dotted lines show how the enhancement ratios of the two radiosensitizers are calculated.

(2) The post treatment delay for tumours treated with radiosensitizer plus radiation is greater than that for tumours treated with the same dose of radiation alone. The effect of misonidazole is greater than that of metronidazole.

To determine the enhancement ratios for the two sensitizers applied, the post-treatment delays for the mean tumour cross-sectional areas, determined directly from Fig. 2, are plotted versus irradiation dose in Fig. 3a. The post-treatment delay for the tumour group irradiated with 1250 rad was determined by backward extrapolation of the regrowth curve as indicated by the dotted line in Fig. 2. In Fig. 3b the mean of the post treatment delays for each tumour is plotted versus dose. The mean post treatment delays were calculated from the regrowth curves for each individual tumour. These regrowth curves are not shown here. For those tumours which did not shrink below their initial sizes, the post treatment delays were determined as in Fig. 2 for the group receiving 1250 rad. The enhancement ratio of metronidazole was determined to be 1.2 and 1.3 from Fig. 3a and 3b respectively. The corresponding values for the enhancement ratio of misonidazole were found to be 1.5 and 1.4.

The enhanced post treatment delay found when a radiosensitizer is used in combination with 1250 rad relative to that for 1250 rad alone, is probably due to enhanced inactivation of hypoxic cells. Since it is likely that almost all well-oxygenated cells are inactivated after an exposure to 1250 rad, the enhanced post treatment delay found when the dose is increased to 1875 rad may also be due to enhanced inactivation of hypoxic cells. From Fig. 2 it can be seen that within the first week after treatment the tumour sizes in animals treated with radiosensitizer plus 1250 rad do not differ from those treated with 1250 rad alone. On the other hand, the tumours in animals receiving 1875 rad, a dose which produces the same post treatment delay as 1250 rad in combination with misonidazole, are significantly smaller than those receiving 1250 rad even at four days after treatment. This suggests that the removal of the cells inactivated when a hypoxic cell radiosensitizer is applied in combination with radiation is not as fast as the removal of the cells inactivated by radiation alone. The present experiments are inadequate to make it possible to explain the reasons for this, but it seems not unlikely that the hypoxic cell radiosensitizers make the cells progress more slowly through the cell cycle. If this proves correct, then the interval is prolonged between the time at which the cells are lethally damaged by irradiation and the time they reach mitosis, are destroyed and can be removed.

This hypothesis is supported by other details in Fig. 2:

(3) For tumours treated with radiation alone the rate of regrowth decreases with increasing dose.

(4) The rate of regrowth of tumours treated with radiosensitizer plus radiation is slower than that of tumours treated with a radiation dose which gives an equivalent post treatment delay without sensitizer. This effect is most pronounced for the sensitizer misonidazole.

This also indicates that a calculation of the enhancement ratios based on the time necessary for the tumours to grow to a larger size than the initial one would have resulted in larger enhancement ratios than those determined from the present analysis. Because the length of the observation period was limited by the time an adequate number of animals appeared healthy, this could not be verified experimentally. Facilities making long-term investigations possible with the mutant nude mouse are now being procured for this institute.

DISCUSSION

In the present investigation the radiosensitizing effect of metronidazole and misonidazole has been tested on a human malignant melanoma grown in the mutant nude mouse. Enhancement ratios of 1.2–1.3 and 1.4–1.5 have been found respectively after single exposures to 1250 rad for these two radiosensitizers. This result indicates that misonidazole is a more efficient hypoxic cell radiosensitizer than metronidazole for human tumours, as has been shown to be the case for various animal tumours.

The numerical values of sensitizer enhancement ratios obtained from *in vivo* studies depends on the fraction of hypoxic cells in the tumour, the experimental conditions and the method of data analysis. Taking this into account, it is evident that the enhancement ratios determined in the present study are in full accord with those determined from studies of transplantable animal tumours (Denekamp and Harris, 1975; Rauth *et al.*, 1975; Fowler *et al.*, 1976a).

Preliminary clinical trials have shown that serum concentrations up to approximately 300 μg/ml for metronidazole (Deutsch *et al.*, 1975; Urtasun *et al.*, 1975) and 200 μg/ml for misonidazole (Gray *et al.*, 1976) will be tolerated in patients. In the present investigation drug doses corresponding to serum concentrations of 500–600 μg/ml for metronidazole and 400–500 μg/ml for misonidazole were applied. However, even at clinically tolerable serum concentrations of metronidazole and misonidazole, appreciable sensitizer enhancement ratios have been obtained from studies of transplantable animal tumours and normal tissue (Stone and Withers, 1974; Denekamp *et al.*, 1974; Rauth and Kaufman, 1975). The high degree of correspondence between the response of transplantable murine tumours and human tumours grown in the mutant nude mouse to radiosensitizers at high serum concentrations indicate that clinically useful sensitizer enhancement ratios also will be observed in human tumours at drug concentration below the tolerance level in man, at least for the radiosensitizer misonidazole. This has also been verified in a small clinical trial carried out at Mount Vernon Hospital, England (Thomlinson *et al.*, 1976).

From a clinical point of view, however, the hypoxic cell radiosensitizers will be of interest only if detectable enhancement ratios can be obtained when the drugs are used in combination with clinically relevant fractionated irradiation regimes. Fowler has used the C3H mouse mammary tumour, a tumour known to reoxygenate rapidly and extensively, to compare the effect of several fractionated irradiation schedules with and without misonidazole. Without sensitizer the effect of the fractionated irradiation was variable and was thought to depend on the degree of reoxygenation. With sensitizer the results were more uniform and the effect upon the tumour larger (Fowler *et al.*, 1976b).

The clinical usefulness of hypoxic cell radiosensitizers may therefore depend on the extent to which human tumours reoxygenate and on the rate of reoxygenation. The present investigation has indicated that this model system (human tumours in the mutant nude mouse) is well suited to clarify the potential usefulness of these radiosensitizers. Studies making use of different tumour types and clinically relevant fractionation schedules are therefore now in progress at our institute.

Acknowledgments

We are grateful to the head of the department of surgery, the Norwegian Radium Hospital, Dr. I. O. Brennhovd, for supplying us with the human melanoma tissue. We are also grateful to Roche Chemical Co. Ltd., Hertfordshire, England, for the generous gift of the sensitizer misonidazole. We acknowledge financial support from The Norwegian Cancer Society, The Norwegian Research Council for Science and the Humanities and The Nansen Scientific Fund.

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Technical note

Preparation of the patient for abdominal ultrasound scanning

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ABSTRACT

The value of dietary restriction and laxatives both separately and in combination for the reduction of bowel gas has been investigated and compared with unprepared patients. No significant difference was found between the results from prepared and un-prepared patients.

The largest single cause of failure to visualize the abdominal organs at ultrasound scanning is the presence of excessive quantities of gas within the bowel. Many regimes for the reduction of bowel gas have been used in radiography, and since we believe that both large and small bowel gas may be causing difficulty in ultrasound patients, we have investigated the efficacy of the standard bowel preparation used in our hospital for upper abdominal X-ray examinations.

MATERIALS AND METHODS

The standard preparation consisted of a fluid only diet for 24 hours before the examination, combined with the administration of two Dulcodos tablets* on each of the two evenings before the examination. Since the aim of the preparation was to reduce both small and large bowel gas, four separate groups of preparation were chosen. Group I had no preparation and acted as controls, Group II had 24 hour fluid diet with no laxative, Group III had normal diet plus laxatives and Group IV had 24 hour fluid diet plus laxatives.

Two hundred consecutive patients presenting for routine liver ultrasound scan after diagnosis of primary breast carcinoma were randomly allocated to each group by drawing one of 200 marked cards from a container, thus giving fifty patients in each group.

The person performing the ultrasound scans had no knowledge of the type of preparation given to each patient. When all two hundred patients had been examined all the films were reviewed by H.M. and scored for gas quantity and examination quality. The scoring system used was: Gas quantity: small 1; moderate 2; large 3. Examination quality: good 1; average 2; poor 3.

The type of preparation given to each patient was then determined and patients' results sorted into the different preparation groups. The total gas score, the total examination quality score and the overall total score for each group was determined and the number of patients with each individual score was also calculated.

RESULTS AND DISCUSSION

The scores for quantity of gas can be seen in Table I and those for examination quality in Table II.

Perhaps the most important figures are the total gas scores for the four groups, 98 ± 1, thus indicating

TABLE I

NUMBER OF PATIENTS WITH EACH GAS SCORE

	1 small	2 moderate	3 large	Total score
No prep.	17	19	14	97
Laxative	21	10	19	98
Diet	16	19	15	99
Both	23	7	20	97
Totals	77	55	68	

TABLE II

NUMBER OF PATIENTS IN EACH EXAMINATION QUALITY GROUP

	1 good	2 average	3 poor	Total scores	Gas + exam score
No prep.	21	19	10	89	186
Laxative	19	20	11	92	190
Diet	23	13	14	91	190
Both	26	14	10	84	181
Totals	89	66	45		

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*Dulcodos® (Boehringer Ingelheim Ltd. Bracknell, Berkshire.) enteric coated tablets, each tablet contains Dulcolax® (bisacodyl B.P.) 5 mg, dioctyl sodium sulpho-succinate 100 mg.

a surprising consistency in the quantities of bowel gas in the patients in the four different groups and a complete absence of any detectable beneficial effect from either form of preparation.

In general the examination quality scores mirrored those for gas quantity very closely though there was a slightly wider variation in the total scores.

Review of the number of patients achieving each score reveals that the largest number of patients in any group were those having the full preparation and achieving best scores (1) for gas (23 patients) and examination quality (26 patients). The effect of this may be seen in the slightly better total examination quality score (84) for patients receiving both forms of preparation but the difference is barely significant.

We therefore do not feel that the types of preparation investigated here are of any value in patients referred for abdominal ultrasound scan.

These findings are in agreement with those of Sommer and Filly (1977), though they had only five patients in each group and their results were therefore statistically less significant.

Despite the lack of efficacy of preparation, 155 patients in this study (77.5%) had a satisfactory (good or average) examination and this proportion has continued unchanged since we discontinued preparation of our patients.

If an efficient regime for gas reduction could be discovered we do not feel we would be justified in applying it wholesale to all patients and consider that it would be better to employ it only on those who have an unsatisfactory scan at their first visit.

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SOMMER, G., FILLY, R. A., 1977. Patient preparations to decrease bowel gas: evaluation by an ultrasonic method. *Journal of Clinical Ultrasound*, *5*, 87–88.

Book review

Practical atlas of cardiac scintigraphy. Editor in Chief, P. de Vernejoul, illust. colour, 1977 (C. V. Mosby Co., St. Louis), $57.50.

This multi-editor multi-author atlas is unusual. Its text has parallel English and French versions and is only 21 pages long. The other 90 pages contain some 110 plates on high quality art paper. There are many colour reproductions of original rectilinear cardiac scans obtained with Thallium 201 or after intracoronary microsphere injections. The black and white presentations of original gamma camera dynamic cardiac cavity results are well portrayed. Those studies with analogue computer assisted display however are less satisfactory.

A particular and most useful feature of the book is a set of loose transparencies which can be set to overlie accurately various plates. For example, the serial scintigraphic images of a gamma camera study may be set up so that the anatomical landmarks and cavity boundaries are demonstrated by the transparency. Line drawings also accompany many of the images. There is a considerable waste of paper. This allows the convenience of having the left hand pages devoted only to figure captions and the right hand pages to the illustrations. However, the space under the picture captions could well have been devoted to a little clinical history, a summary of the findings (ECG, enzymes etc.) and a note on the benefit if any that the scan contributed to the management of the patient.

The strength of the book lies in its qualities as an atlas of the range of normal and abnormal results of scanning the heart in all the usual projections. There is a particularly helpful section on the individual and combined intracoronary artery injections of $^{113}\text{In}^{\text{m}}$ transferring microspheres and $^{99}\text{Tc}^{\text{m}}$ albumin microspheres. There is a strong section on the classical angioscintigraphic appearances of the congenital heart abnormalities and acquired valvular disease. There is however no attempt at quantitation of any of the dynamic or static images. This and the emphasis on the use of the rectilinear scanner probably reflects the gestation time of the atlas. As a reference manual for the radiologist and radiologically orientated cardiologist, it succeeds in getting over the meanings of the various patchworks of coloured lines and black and white dots that make up the images. Both by intent and content it does not however meet the need of the practitioner of nuclear medicine who desires a physiological approach to the measurement of cardiac function with radionuclides.

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1978, *British Journal of Radiology*, *51*, 389–391

MAY 1978

Case report

Lymphographic opacification of liver and spleen

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(*Received September, 1977*)

Liver opacification after lymphography by the pedal route is a rare occurrence and splenic opacification has not been previously reported.

CASE REPORT

A 34-year-old man presented with a three months' history of enlargement of the lymph nodes on the left side of the neck. Physical examination was otherwise normal. There was no history or physical evidence of alcoholism, liver disease or obstructed venous or lymphatic drainage.

Biopsy of an enlarged node revealed nodular sclerosing Hodgkin's disease. Chest radiograph, full blood count, bone marrow biopsy and liver function tests were all normal.

Bipedal lymphography was performed, infusing 7 ml of ultra-fluid Lipiodol on each side. The initial radiographs taken at the end of the infusion showed diffuse opacification of both liver and spleen (Fig.1). The pattern of this opacification was typical of the arborization of the blood vascular system and at 48 hours it had become more peripheral (Fig. 2). No lymphatic channels leading to liver and spleen were opacified even though the iliac and lumbar lymphatics were well filled on the initial radiographs.

There was evidence of lymphatic obstruction in the upper lumbar area with reflux of contrast into lymphatics not normally filled, lying lateral and anterior to the lateral lumbar chains (Fig. 3). Lumbar ducts leading towards the

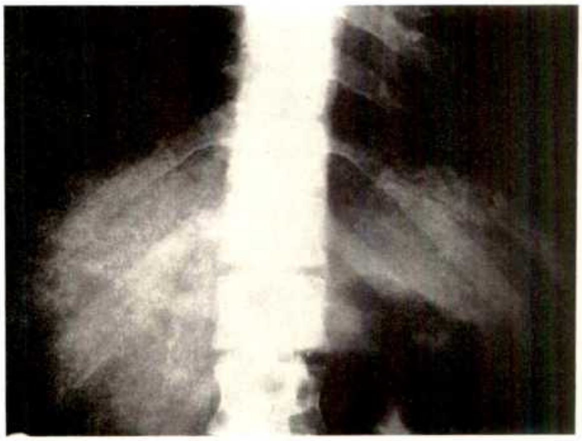

FIG. 2.

Forty-eight hours later, the opacification has become more peripheral.

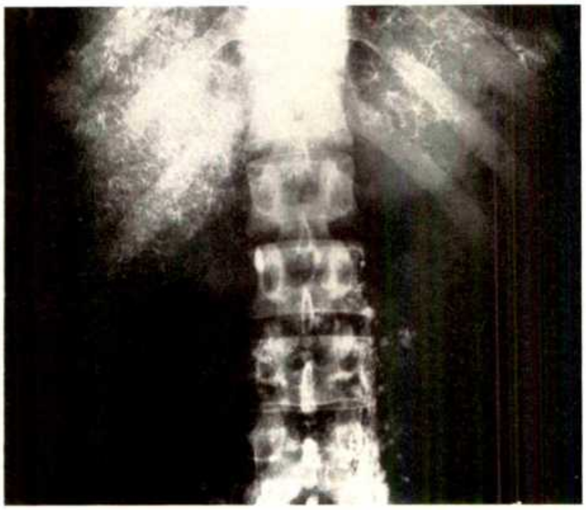

FIG. 1.

At the end of the bipedal infusion, there is already dense arborizing opacification in both liver and spleen.

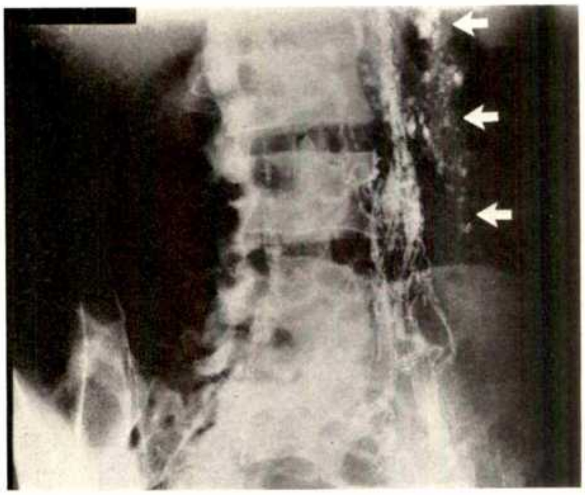

FIG. 3.

Oblique film at the end of infusion shows reflux into lymphatics that are not normally filled (arrows), lying lateral and anterior to the left lumbar chain.

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cisterna chyli were dilated and one of them still contained a little medium at 48 hours. Obstruction was not complete however and some contrast flowed into the thoracic duct which appeared normal and not dilated.

Liver opacification was still present, though greatly faded, at three months. Following staging laparotomy with splenectomy two weeks after the lymphogram, the left subphrenic opacification abruptly disappeared proving it to have been in spleen and not in left lobe of liver.

The laparotomy revealed macroscopically abnormal supraduodenal nodes which on biopsy were shown to be infiltrated by nodular sclerosing Hodgkin's disease. The excised spleen was also heavily infiltrated, though of normal size and weight. The liver was macroscopically normal and multiple liver biopsies were clear of lymphoma and cirrhosis.

There were no findings at operation to suggest any degree of portal hypertension or of inferior vena cava obstruction.

Histology showed vacuoles due to Lipiodol in the excised lymph nodes as is normal after lymphography, but also revealed such vacuoles in the portal areas of the liver and in the spleen. It was impossible to determine from microscopy exactly which vessels contained the Lipiodol droplets.

DISCUSSION

Hepatic opacification via lymphoportal communications

Post-natally, the entrance of the thoracic duct and of the right lymphatic duct into the great veins at the root of the neck are the only functioning lymphovenous communications. However, when lymphatic drainage is blocked and pressure rises, other existing lymphovenous communications open up; these have been found in the abdomen, pelvis and lower limbs (Threefoot *et al.*, 1963; Yoffey and Courtice, 1970; Kinmonth, 1972b).

Liver opacification by pedal lymphography has been recorded in occasional case reports of obstruction of the lumbar lymphatic chains. In some of these (Perez-Tamayo *et al.*, 1963; Chavez *et al.*, 1965; Bodie and Linton, 1971) there was also obstruction of the inferior vena cava or common iliac veins and it was thought that the contrast had to pass first of all into systemic veins and then, because of the block here too, via the haemorrhoidal plexus into the portal venous system. However, systemic venous obstruction was not present in other cases (Leger *et al.*, 1961; Herman *et al.*, 1964; Wallace *et al.*, 1965; Hecht *et al.*, 1968; Kinmonth, 1972a; Besson and Delaneau, 1972) or in our own.

There are other considerations also supporting liver embolization via direct lymphoportal communications:

(1) if lymphatics had carried the Lipiodol retrogradely to the liver, they should have been visualized at some stage because of the slow flow even in non-obstructed "antegrade" lymphatics;

(2) venous flow is very much faster and one would not expect to see opacification of the veins leading to the liver because of the very small quantity of medium injected; we have for instance never visualized the great veins in the upper thorax even with good opacification of the thoracic duct draining directly into them;

(3) lympho-arterial communication is clearly impossible because of the much higher arterial pressure;

(4) Chavez *et al.*, (1965) injected Lipiodol into the inferior mesenteric vein of dogs and produced liver opacification identical to that in our case.

Splenic opacification by hepatofugal flow due to hepatic embolization

There was no opacification of lymphatics leading to the spleen, and in fact the spleen contains hardly any lymphatics (Raviola, 1975). The only possible route therefore was by retrograde flow in the splenic vein, even though it was obvious from the clinical and laparotomy findings, and examination of liver biopsies and excised spleen, that the patient did not suffer from cirrhosis or portal hypertension.

However the density of the liver embolization (Figs. 1 and 2) was much greater than that of the pulmonary embolization pattern usually seen after lymphography. Yet even in the lungs with their much larger vascular bed, the reduced capillary volume after lymphography is sufficient to cause a clinically significant fall in diffusing capacity (Gold *et al.*, 1965; Weg and Harkleroad, 1968; White *et al.*, 1973) and a rise in pulmonary artery pressure giving an increased diameter of the descending pulmonary arteries (Weg and Harkleroad, 1968).

It is not difficult therefore to postulate that the massive embolization shown in Figs. 1 and 2 into the much smaller hepatic portal bed caused an acute, transient rise in portal venous pressure with hepatofugal flow in the splenoportal venous axis.

Chavez *et al.*, (1965) found Lipiodol thrombi in the portal venous radicles after injection into the inferior mesenteric vein of dogs, and interpreted the concomitant distension of the lymphatics (at histology) as being due to the resulting portal hypertension.

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Book reviews

The physical principles of diagnostic radiology. By Perry Sprawls, Jr, pp.ix+365, illust., 1977 (University Park Press, Baltimore), $24.50, £17·50.

This book gives the physical principles underlying diagnostic radiology and includes a chapter on ultrasound but does not cover nuclear medicine. It is based on the training programme of the Department of Radiology of the Emory University School of Medicine. It covers the theoretical and practical production of X rays and their interaction with matter. Penetration, scattered radiation and image contrast are discussed together with film density control and film characteristics. Image blurr and resolution, the focal spot, intensifying screens and intensified radiography and image noise are also covered. Fluoroscopy, tomography and patient and personnel exposure are dealt with. The measurement of X-ray quantities and units are described. There is an appendix on mathematical relationships in radiology for those not familiar with these. The book thus gives a good theoretical background to the subject. It is perhaps a little unfortunate that it has appeared just after the introduction of SI units to radiology, otherwise it is up-to-date.

It would have been a great help to have had a chapter on SI units since these are not familiar to everyone and this might have improved the statement that "heat is usually expressed in the units of joules (watt-seconds)". The work is designed to be a theoretical introduction to the subject and at least in the reviewer's opinion it is a pity that it does not give more indication of practical applications as to how certain parameters might be checked in practice. As an example, when discussing contact between film and intensifying screens it indicates that the usual test for adequate contact is to radiograph a wire mesh. It gives no indication that there is an IEC standard method. It is stated that kVp is normally measured by using "a so-called Adrian Crooks type cassette". The description is that of the Sisconsin modification but it is doubtful if anyone not familiar with this item would be able to follow the description. A few more references might have been given and some of those given require checking. There are many other points of a similar nature which could be criticised but despite this the book gives a useful background for those training in diagnostic radiology.

G. M. ARDRAN.

Paleopathological Diagnosis and Interpretation. By R. T. Steinbock and T. Dale Stewart, pp. xvi+423, illus., 1976 (C. C. Thomas, Springfield, Illinois), $22.75.

The scientific investigation of human archaeological remains, while primarily the concern of the anthropologist and archaeologist, is increasingly involving the interests and skills of the radiologist and pathologist.

The study of disease in antiquity is properly directed towards the establishment of patterns of morbidity and health care in ancient communities and their influence on cultural development. A basic standard of knowledge of the pathological processes to be encountered is, however, as important to the anthropologist as an insight into the aims and objectives of the total study is to the interested radiologist or pathologist. It is encouraging, therefore, to find a book which, without compromise, takes a multidisciplinary overview approach to the problem.

Much of our knowledge of paleopathology has been gained from the studies of excavated skeletal and mummified material. Attention has been directed in *Paleopathological Diagnosis and Interpretation* to the bony skeleton using the large collections of several American institutions including the Smithsonian to obtain correlative morphological, radiological and pathological studies.

Each chapter deals with a special aspect of bone disease in antiquity including its epidemiology. The major infections, tumours and trauma, together with haematological and metabolic bone disorders are considered. One chapter is devoted to joint disease and the book is introduced by a short dissertation on bone as a living tissue. In each section the presentation is clear and informative with key references to many aspects of the disciplines involved.

The volume is directed towards all those concerned with the diagnosis and interpretation of bone lesions in excavated specimens. The scope of discussion is on occasion limited and one might criticize the quality of reproduction of some of the radiographs but the book can certainly be recommended to the radiologist who is in any way interested in archaeology.

The trainee radiologist might read it with profit and not a little pleasure.

IAN ISHERWOOD.

1978, *British Journal of Radiology*, *51*, 392–393

Short communications

A comparison of the biological effect of iodine 125 and tantalum 182 gamma rays using *vicia faba* roots

By E. R. Hering, M.Sc., Ph.D., M.I.Biol., M.Inst.P., P. L. M. Le Roux, M.Sc., Ph.D., F.Inst.P., M.(S.A.)I.E.E., and R. Sealy, M.Med.(Rad.T)., F.R.C.R.

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(*Received April, 1977 and in revised form January, 1978*)

Seeds containing iodine 125 as supplied by Lawrence Soft Ray Corporation have now been used at this hospital to treat a variety of patients with tumours which would have been treated with applicators or moulds loaded with ^{182}Ta or ^{226}Ra if the seeds had not been available. Iodine seeds have also been extensively used at other hospitals, *e.g.* Kim and Hilaris (1975), Hilaris (1976), and Charyulu *et al.* (1976). The advantages of ^{125}I over ^{182}Ta have already been outlined earlier (Sealy *et al.*, 1976; Hering *et al.*, 1977). However, whereas the radiobiological effectiveness (RBE) of the ^{182}Ta radiation relative to 250 kV X rays is well known, there is at present no such information available for ^{125}I. By considering the LET spectrum of the X rays of ^{125}I, Kim and Hilaris (1975) have predicted an RBE of the seeds for human tumours higher than one and less than 1.5. Some radiobiological studies are needed to test this prediction and this has led to some preliminary investigations on *vicia faba* as outlined below.

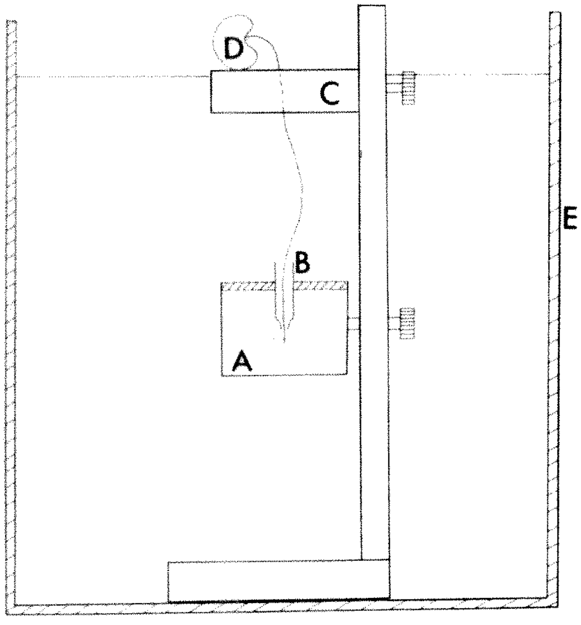

Fig. 1.

Schematic diagram of the irradiation jig used for the irradiations with ^{182}Ta and ^{125}I.
(A) Perspex ring holding the iodine seeds or tantalum wire. The level of the source(s) is given by the dotted line. (B) glass tube to hold root tips in position opposite the radiation source(s). (C) support for seedlings. (D) seedling. (E) tank filled with water at 3.5°C.

Materials and Methods

Seed of *vicia faba* (variety" Aquadulce") was germinated and the roots grown in water at 19°C±0.2°C as described previously (Hall *et al.*, 1962). The roots were then transferred to water at about 3.5°C for one day before being irradiated with ^{182}Ta or ^{125}I. All irradiations were carried out in water at 3.5°C±0.2°C to avoid any appreciable growth of the roots during the relatively long irradiation periods. The roots were measured and returned to 19°C after irradiation for the ten day growth. The control roots were treated in the same way and remained in the cold water for the same period as the irradiated roots. A specific control group was used for each irradiation time.

The jig used for the irradiation of the roots at 2.3 cm from the source is shown in Fig. 1. The seedlings (ten) were positioned on the jig as shown, so that the root tips were at the centre of a ring of 14 ^{125}I sources or ^{182}Ta wire embedded in a groove cut into the surface of the perspex ring. The distance from the root-tips to the radioactive sources was 2.3 cm.

TABLE I

Value of G_{10}, the growth in ten days of the roots exposed to the radiation of ^{125}I and ^{182}Ta expressed as a fraction of controls of equal age. The treatment distance was 2.3 cm. Each value of G_{10} is the mean of ten roots.

Radiation modality	Dose rate (rad/hr)	Dose (rad)	G_{10}
^{125}I	9.0	33.7	0.98±0.07
	10.5	72.1	0.91±0.04
	8.4	109.1	0.78±0.09
	6.3	133.7	0.68±0.04
	8.1	160.3	0.59±0.03
	3.7	186.0 (±3%)	0.65±0.05
	6.4	237.1	0.50±0.05
	5.1	245.1	0.36±0.04
	4.2	297.7	0.26±0.04
	4.4	306.5	0.26±0.04
	5.5	340.6	0.28±0.02
^{182}Ta	8.1	63.1	0.98±0.06
	8.7	135.1	0.69±0.05
	8.2	204.2	0.68±0.05
	6.8	250.3 (±2%)	0.56±0.05
	7.0	299.6	0.53±0.03
	7.2	253.4	0.50±0.04
	6.0	418.3	0.40±0.05
	6.6	457.5	0.25±0.02

*The errors in G_{10} are standard errors of the mean.

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The doses quoted in Table I represent values calculated for the specified root-to-source distance. The doses to the roots were calculated using the method described by Anderson and Ding (1975). The variation in the dose to the roots is caused by slight variations in the root-to-source distance. The percentage errors in column three of Table I represent maximum variations in the values for the dose.

RESULTS AND DISCUSSION

The growth of the roots in ten days for the ^{125}I and ^{182}Ta irradiations at similar dose rates and for the same root-to-source distance of 2.3 cm show that there is an increase in the damage caused to the roots by ^{125}I compared with ^{182}Ta (Table I). The results were analysed with the Pike-Alper program (Pike and Alper, 1964) and the RBE of ^{125}I relative to ^{182}Ta was found to be 1.70 with 95% confidence limits 1.22–2.48. Graphs presented by Kohn (1958) suggest that various biological systems each exhibit a response to a particular radiation modality which is unique to that particular system. Thus, the results obtained here are not necessarily applicable to tumours of patients treated with ^{125}I. The value of 1.7 fits in reasonably with the findings of Zeitz *et al.* (1977) who used a simulated ^{125}I spectrum and found a RBE (relative to ^{60}Co) of about 1.4 at very much higher dose rates on HeLa cells.

Since the ^{125}I seeds have been used at this hospital mainly for the treatment of surface lesions, further studies are necessary in order to obtain useful RBE values for these treatment distances of about 5 mm as there is the possibility of a change in quality of the radiation with distance from the source. It may also be necessary to investigate whether the response of mammalian cells is similar to that of *vicia faba*.

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Correlations in bone mineral measurement using polychromatic X rays

By M. I. Al Jarallah, M.Sc. Ph.D., J. A. Archer-Hall, M.A., B.Sc., M.R.C.S., L.R.C.P., and P. E. Francois, B.Sc., Ph.D., F.Inst.P.

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(Received October, 1977 and in revised form December, 1977)

Several techniques have been described in which bone mineral content is assessed by scanning a bone with a narrow beam of monoenergetic photons derived from a radioisotope source, commonly either ^{241}Am or ^{125}I. For some of these techniques measurements have been made of the correlations between bone mineral assessed by photon absorption and the dry weight or ash weight of excised bone samples. The method described by Archer-Hall *et al.*, (1973) is similar except that it takes advantage of the high flux of polychromatic X rays available from a conventional medical X-ray set. A step wedge of an artificial bone-like material fabricated from inorganic salts and epoxy resin is used as a standard; it has a known atomic composition similar to compact bone and a density of 1.73 g/cm^3. Bone mineral estimates are made by scanning the ulna 3 cm from the ulnar styloid. As in the techniques using monoenergetic photons the transmitted intensity is displayed graphically as a trace whose area gives the total mass of bone in the section scanned. This is expressed in terms of mass of the standard step wedge material. In this paper we present correlations of mineral measurements observed using this technique with the bone weight, dry fat-free bone weight and ash weight of the bone, and with the calcium content as measured by

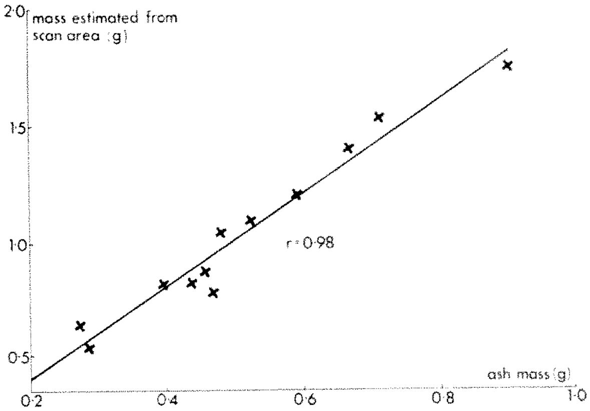

FIG. 1.

The correlation of bone mass estimated from scan area and ash mass.

neutron activation analysis. Comparison, where possible, with measurements made using monochromatic photons allows the performances of the two techniques to be compared.

CORRELATION MEASUREMENTS

For the correlation measurements a number of sections of ulna were obtained post-mortem, from which samples 9 mm long were cut. The pieces were fixed in turn in a plastic jig which enabled them to be held in the normal scanning position in 4.5 cm of saline solution as used clinically. The bone pieces were slightly shorter than the slit length to ensure that they were scanned in their entirety. After scanning, some were ashed by baking at 850°C for two hours.

The correlation between the ash weights and bone mass estimated from the scans is shown in the figure. The correlation coefficient of these measurements is $r=0.98$. This is very similar to the value of $r=0.99$ found by Cameron *et al.*, (1968) using monochromatic photons from ^{125}I, and to the values between 0.97 and 0.95 found by Shimmins *et al.*, (1972). Both of these groups of workers made observations on sections of radii. Comparisons have also been made between the scan areas and bone weight, and dry fat-free bone weight, both giving correlation coefficients of $r=0.96$. In addition the calcium content of a number of specimens has been measured by neutron activation analysis. This was done by observation of the ^{49}Ca activity produced by the reaction $^{48}Ca(n, \gamma)^{49}Ca$ using the facilities of the Universities Research Reactor, Risley. The poorer correlation coefficient $r=0.83$ obtained from these measurements may be due to the larger uncertainties associated with the neutron activation analysis.

ACKNOWLEDGMENTS

We should like to thank Dr. A. W. Downs of the Chemistry Department, University of Aston, and Dr. P. B. Carpenter of the Radiology Department, Dudley Road Hospital, for their help.

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Analysis of publication, 1977

The table below gives an analysis of papers which appeared in volume 50 of THE BRITISH JOURNAL OF RADIOLOGY (1977). It is in the same form as the table for volume 49 which appeared on page 609 of volume 50 (September 1977). The distribution among subject matter is quite similar.

ANALYSIS OF PAPERS IN THE BRITISH JOURNAL OF RADIOLOGY DURING 1977 INCLUDING TECHNICAL NOTES AND CASE REPORTS BUT EXCLUDING SHORT COMMUNICATIONS, LETTERS TO THE EDITOR AND RADIOLOGY NOW

Category	Number of contributions	Number of pages	Pages per contribution	Per cent of total	
				contributions	pages
Diagnosis by X rays excluding case reports	54	269	5.0	32	36
Case reports (X-ray diagnosis)	33	67	2.0	20	9
Diagnosis by ultrasonics	5	22	4.4	3	3
Diagnosis by nuclear medicine	13	55	4.2	8	7
Thermography	1	2	2.0	1	0
Radiotherapy	9	41	4.6	5	6
Physics	11	54	4.9	6	7
Radiobiology	17	110	6.5	10	15
Radiation hazards	5	30	6.0	3	4
Nuclear medicine with physics	5	21	4.2	3	3
X-ray diagnosis with physics	5	31	6.2	3	4
Radiotherapy with physics	3	18	6.0	2	2
Ultrasonics with others	4	15	3.8	2	2
Other combinations	3	16	5.3	2	2
Total	168	751	4.5	100	100

1978, *British Journal of Radiology*, *51*, 395 May 1978

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents).

The Editor—Sir,

Statements of the MRC Isotope Panel

We have noted the strong reaction of the Council of the British Nuclear Medicine Society (Croft and Maisey, 1978) to our paper on the "ten-day rule" and its possible relevance to nuclear medicine. This reaction would appear to contradict the current advice given in ICRP 26 para. 206, the NCRP Report No. 53, and the WHO Technical Report Series No. 611. All these publications emphasize the need to consider what action should be taken to avoid irradiation of the embryo particularly in its early stage of development.

Croft's assertion that the Tri-state study (Graham *et al.*, 1966 and Gibson *et al.*, 1968) indicated that irradiation of the ovum prior to fertilization was just as detrimental as irradiation of the embryo does not appear to be supported by the NCRP Report.

Our aim was therefore directed to identifying the situstions where implementation of the "ten-day rule" might be appropriate in nuclear medicine. We pointed out that for our class 'C' patients, in whom investigations are required for their proper management, the criteria for the limitation of dose were those given in ICRP 17 viz. "that the activity administered should be the minimum consistent with adequate information for the diagnosis or investigation concerned". We superimposed on this basic premise the recommendations that we considered made sense in the complex situation of the extended irradiation from radiopharmaceuticals.

The table of typical administrations was compiled from the large number which had been submitted for approval by the MRC Isotope Advisory Panel. We are only too well aware that different procedures call for different administrations of the same radiopharmaceutical, that the same procedure might call for different activities in different centres depending on the available equipment and expertise, and also that the Panel's advice was not always sought or followed.

With regard to the use of thyroid blocking agents the view expressed on behalf of the British Nuclear Medicine Society that the routine use of these agents is difficult to justify needs further scientific debate. It is contrary to the policy which has been adopted by the MRC Panel over the last 25 years, and it might be noted that we have suggested a number of examples to indicate where this policy could be relaxed. We would agree, however, that our recommendations concerning ^{99}Tc^{m} radiopharmaceuticals should be regarded as applying primarily to pertechnetate, and that notwithstanding the numerous references in the nuclear medicine journals and in manufacturers' pack leaflets the use of sodium perchlorate is preferable to that of potassium perchlorate.

Yours, etc.,

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B. E. C. Nordin,
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WHO, Technical Report Series 611, 1977. Use of Ionizing Radiation and Radionuclides on Human Beings for Medical Research, Training and Nonmedical Purposes.

ICRP Publication No. 26, 1977. Recommendations of the International Commission on Radiological Protection. Annals of the ICRP, Vol. 1, No. 3.

The Editor—Sir,

The Centigray as the S.I. Unit of Dose

I wish to ask for support for the use of the centigray (cGy) as the practical S.I. unit of dose for clinical radiotherapy. This proposal has two obvious advantages. Firstly, and most importantly, the centigray is identical numerically with the rad. Secondly, its use will circumvent any tendency to lower standards of accuracy that might follow use of the gray itself, 100 times larger. There should be no practical difficulties in this any more than in the continued use of the centimetre for length.

Yours, etc.,

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The Editor—Sir,

Upper Gastrointestinal Tract Visualization as an Aid to the Interpretation of Pancreas Scintigrams

In a recent note Cox *et al.*, (1977) underline the importance of the well known problem of distinguishing the pancreas image from that of the upper gastrointestinal tract due to the accumulation of the marker (^{75}Se-methionine) in the stomach and the upper part of the small bowel. In order to be correct, this note needs the following comments:

1. Specific uptake of ^{75}Se-methionine was described initially by Bühring and Schneider (1967).
2. Our laboratory elaborated an original technique in order to eliminate the GI-tract image by subtraction (Henry *et al.*, 1972; Frühling and Henry, 1974). According to our technique, stomach, duodenum and the upper part of jejunum were visualized by ^{99}Tc^{m}-pertechnate given orally. Clinical results obtained by this technique were published in two papers (Frühling and Balikdjian, 1974; Frühling *et al.*, 1975) and in a review article (Frühling, 1976).
3. Independently, Black (1973) published four years ago a method for determination of the position of the head of the pancreas by visualizing the duodenal loop after oral administration of ^{99}Tc^{m}-pertechnate.
4. Duodenal visualization is only one part of the problem. Stomach uptake often overlies the image of pancreatic corpus and cauda. In these cases upper GI-tract *subtraction* is an absolute necessity.

5. From a technical and scintigraphic point of view the use of ^{99}Tc^{m}-pertechnate or colloid are equivalent.

Yours etc.,
J. Frühling.

Laboratoire des Radio-Isotopes,
Institut Jules Bordet,
Faculté de Médecine,
Université Libre de Bruxelles,
1000 – Bruxelles,
Belgium.

REFERENCES

Black, M. B., 1973. Analysis of pancreas scintiphotos. *Journal of Nuclear Medicine*, *14*, 246.

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(*in reply*)

The Editor—Sir,

Upper Gastrointestinal Tract Visualization as an aid to the Interpretation of Pancreas Scintigrams

The purpose of our communication was twofold. First, we wished to bring to discussion observed differences in the clinical performance of synthetic selenomethionine as compared with biosynthesized material. The review of Bühring and Schneider quoted by Dr. Frühling was written long before *synthesized* material was available. As far as we can ascertain, our results are the only clinically verified data available on synthetic selenomethionine. Second, we wished to point out that the use of duodenal visualization as an adjunct to pancreas scintigraphy can be helpful and we are pleased that Dr. Frühling subscribes to this view. Nevertheless the technique of Black, as confirmed by Dr. Frühling himself, suffers from the disadvantage that pertechnetate becomes bound to the gastro-intestinal mucosa which may hinder passage into the duodenum and can lead to uneven distribution in the G.I. tract which can be difficult to interpret on a scintigram. The use of technetium colloid on the other hand eliminates this problem. The activity freely mixes with the stomach contents and moves unhindered through the gastrointestinal tract. There is also no transport of activity across the intestinal mucosa into the bloodstream which may occur with pertechnetate. For this reason it can be claimed that colloid is the reagent of choice for this study.

Yours, etc.,
P. H. Cox,
H. S. L. M. Tjen,
W. B. van der Pompe.

Rotterdamsch Radio-therapeutisch Instituut,
Groene Hilledijk 301,
Rotterdam, The Netherlands.

The Editor—Sir,

Narrow-Needle (Chiba) Cholangiography

In response to the article by Jain *et al.*, 1977 and the ensuing letter (Carty and Markham, 1977), we wish to make some observations based on our own experience of narrow-needle cholangiography. Our preliminary experience has been published elsewhere (Bass and Shaff, 1976; Schulman and Bass, 1977).

We have now done over 100 cases. Our success rate in obstruction, even in those cases where the obstruction was only moderate and the intrahepatic ducts not convincingly dilated, has been 100%. Successful bile duct entry has almost always been achieved at the first or second pass. In cases where there has been no obstruction whatsoever, our success rate has been of the order of 50%.

In some of our initial patients, operation was delayed for several days; we did, in a number of these, encounter instances of septicaemia and of peritoneal bile leak in the presence of obstruction. We therefore now routinely use Ampicillin and Gentamycin cover and perform the examination immediately before operation. No complications have occurred in the absence of obstruction.

Yours, etc.,
A. Schulman,
M. Goldblatt,
M. I. Shaff.

Department of Radiology,
Groote Schuur Hospital,
Cape Town,
South Africa 7925.

REFERENCES

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The Editor—Sir,

Faster Contrast Passage Through a Chiba Needle in Percutaneous Trans-Hepatic Cholangiography

The letter by J. K. Millar (1977) makes the useful suggestion of injecting a low viscosity contrast medium in order to obtain adequate visualization of the biliary tree when using the fine gauge 23–25 s.w.g. 14 cm long Chiba needle.

Dr. Millar suggests the use of Urografin 150. Unfortunately, Dr. Millar does not consider the fundamentals influencing viscosity of intravascular contrast medium and therefore he makes an erroneous conclusion and recommendation.

Correspondence

There are three basic factors influencing the viscosity of current intravascular contrast media:

1. The concentration of the solution, both mg iodine per ml and weight of salt per volume of solvent.
2. The anion, *i.e.* the iodinated radicle. All current urographic contrast media employ very similar iodinated substituted benzoate anions—diatrizoate (Hypaque, Urografin), iothalamate (Conray), metrizoate (Triosil). Solutions of these ions have almost the same viscosity for equivalent iodine content.
3. The cation. Two cations are in current use—sodium (low molecular weight and low viscosity) and meglumine (higher molecular weight and higher viscosity).

It is obvious therefore that to provide a solution of current contrast media of the lowest viscosity for any required iodine content—the only variable is the cation content. A sodium solution provides much the lowest viscosity.

Dr. Millar suggests Urografin 150 which provides an iodine concentration of 146 mg per ml. Unfortunately, this is *not* a low viscosity medium for its constituent salts are 0.26G meglumine diatrizoate and 0.04G sodium diatrizoate, that is, it is 87% meglumine salt. A sodium solution of the same iodine concentration would provide a solution of lower viscosity. Such a medium is Hypaque 25% which contains 150 mg iodine per ml and contains only sodium and no meglumine cations.

The relative viscosities at 37°C are Urografin 150→1.4 C.P. and Hypaque 25%→1.09 C.P.

In fact, for solutions of this low iodine content, viscosity is not a very important factor, but the underlying principles influencing viscosity of intravascular contrast agents are very important for urography and angiography.

It is in order to emphasize these important fundamentals, that this letter is submitted.

Yours, etc.,
R. G. GRAINGER.

X-ray Department,
The Royal Hospital,
West Street,
Sheffield S1 3SR.

REFERENCE

MILLAR, J. K., 1977. Faster contrast passage through a Chiba needle in percutaneous trans-hepatic cholangiography. *British Journal of Radiology*, *50*, 598.

THE EDITOR—SIR

INCREASED FILTRATION DUE TO TUNGSTEN DEPOSITS INSIDE THE ENVELOPES OF X-RAY TUBES

Reduced output from X-ray units is often attributed to increased filtration due to tungsten deposits inside the tube envelope (Dunlap, 1977).

During 12 years of full-time radiation survey work I have measured the output and quality of radiation under standard conditions and excitation voltage of all the X-ray installations in my area and have not detected any significant change in HVT, even on the most heavily used units, from the value when the tube was new to that after as many as 200000 exposures. The largest change was from 2·6 to 2·65 mm Al, *i.e.* 0.05 mm Al (within experimental error for a poorly regulated unit). My measuring technique has been constant throughout using the same aluminium filters, standard jig, chamber and dosimeter at 80 kV estimated from Ardran penetrameter results and direct measurement.

The roughened state of the anode has also been given as the cause of low output, but one would expect a harder beam if the reduced output were due to craters in the anode; as stated above this has not been found.

I strongly suspect that the effect of tungsten deposits was indeed significant in early stationary anode tubes when the filament assemblies were unshielded, and that this is no longer true. Perhaps repeated mention of these deposits as a cause of low output or beam hardening is no more than folklore? I would welcome any references to recent work which could substantiate statements that in modern tubes an appreciable increase in filtration is commonly due to tungsten deposits.

Yours etc.,
J. W. ADDY,
Radiation Survey Technician.

Medical Physics Department,
Hull Royal Infirmary (Sutton),
Saltshouse Road,
Hull HU8 9HE

REFERENCE

DUNLAP, J. H., 1977. Survey form and techniques for fluoroscopic installations with undertable tubes. *Health Physics 33*, 3–12.

THE EDITOR—SIR,

THE PHOTON ATTENUATION AND ABSORPTION PROPERTIES OF CLEAR AND WHITE POLYSTYRENE

For many years clear polystyrene $(C_8H_8)_n$ has been used in electron dosimetry as a water or muscle substitute, and documents such as the SCRAD "Protocol for the Dosimetry of High Energy Electrons" (SCRAD, 1966) recommend the use of polystyrene calibration phantoms. Unfortunately, the "muscle equivalence" for low energy photons is poor, with the material having both mass attenuation and energy absorption coefficients (μ/ρ, μ_{en}/ρ) differing by more than 20% from the values for muscle at energies below 40 keV.

An interesting improvement in the photon characteristics has been noted with the opaque, white polystyrene, which contains a fine particulate filler of titanium dioxide (TiO_2) in concentrations apparently up to 4% by weight.

Values of μ/ρ and μ_{en}/ρ have been calculated for different concentrations (0–4%) of filler using the conventional addition rule for compounds and the elemental cross sections of Hubbell (1969) and Storm and Israel (1970). The calculated data were compared with similar data calculated for the muscle formulation quoted by ICRU (NBS, 1964). The ratios (μ/ρ) compound/(μ/ρ) muscle and (μ_{en}/ρ) compound/(μ_{en}/ρ) muscle, over the energy range 10 keV–100 MeV, are plotted in Figs. 1 and 2 respectively. As the TiO_2 concentration (by weight) increases, both the low and high energy "equivalence" improves, the low energy region more rapidly, due to the stronger Z-dependence of the filler. The values of μ/ρ for unfilled polystyrene are within 5% of those for muscle from approximately 90 keV–7 MeV, while μ_{en}/ρ

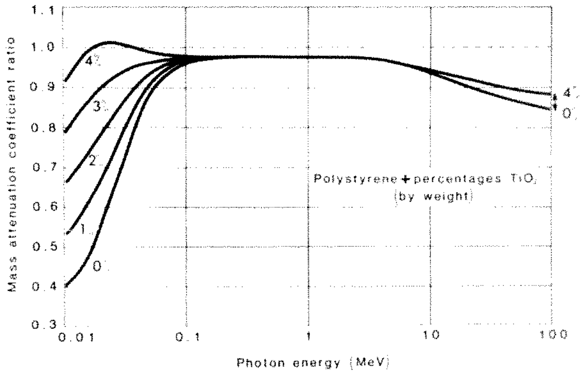

FIG. 1.

Mass attenuation coefficient of unfilled and filled polystyrene relative to muscle.

1978, *British Journal of Radiology*, *51*, 398–399

Correspondence

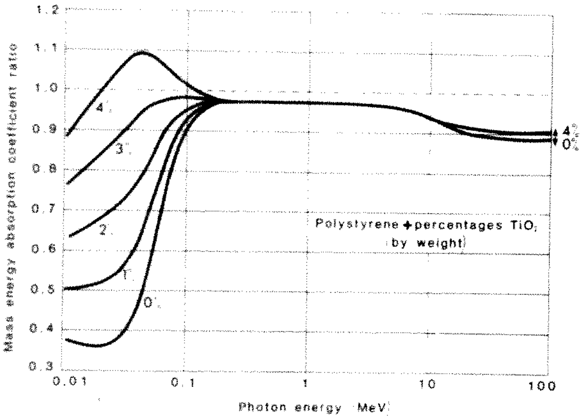

FIG. 2.

Mass energy absorption coefficient of unfilled and filled polystyrene relative to muscle.

values are within the same limits from 130 keV–7 MeV. If 3.7% by weight of TiO_2 is added to polystyrene, μ/ρ is within 5% of that of muscle from 15 keV–10 MeV and μ_{en}/ρ is within 5% from 20 keV–8 MeV.

The electron mass stopping powers (S/ρ) for unfilled polystyrene are within 10% of similar data for muscle over the energy range 10 keV–100 MeV, and within 5% of muscle from 10 keV–20 MeV. When 3.7% TiO_2 is added, the stopping powers are within 8% over the complete energy range, while the 5% energy limits remain essentially unchanged. Electron mass angular scattering powers $(\bar{\Theta}^2/\rho l)$ also show a small improvement when TiO_2 is added. Over the energy range 10 keV–100 MeV, the unfilled polymer has $\bar{\Theta}^2/\rho l$ values within 18–20% of those for muscle; when 3.7% is added, the agreement changes to 14–16%.

Specific gravities vary from 1.05 for unfilled polystyrene to 1.08 for the filled (3.7%) materials. These values compare with a specific gravity of 1.04 quoted for muscle (skeletal) by ICRP (1975). By adjusting the amount of additive, linear attenuation coefficients, μ, may be matched with those for muscle by balancing the effect of the elevated mass density for the filled polystyrene against the μ/ρ values. This may be achieved by plotting graphs of μ against TiO_2 concentration for the energies of interest and selecting the concentration that corresponds to the required μ value for muscle.

Generally, suppliers do not specify the concentration of filler used, but test samples of polystyrene with the 3.7% by weight of TiO_2 have recently been obtained from BP Chemicals Ltd. Preliminary radiographic and CAT scanning measurements on the samples confirm the theoretical data outlined in this correspondence, suggesting that the material might be useful for dosimetric or radiographic investigations in diagnostic radiology.

Yours, etc.
D. R. WHITE.

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13 Bartholomew Close,
London EC1A 7BE.

REFERENCES

HUBBELL, J. H., 1969. Photon cross sections, attenuation coefficients and energy absorption coefficients from 10 keV to 100 GeV. National Bureau of Standards, NSRDS–NBS 29.

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THE EDITOR—SIR,

ELKIND RECOVERY AND "SUB-LETHAL DAMAGE": A MISLEADING ASSOCIATION?

Dr. Alper's closely argued hypothesis (Alper, 1977) makes fascinating reading. Some of her arguments would undoubtedly command general acceptance but others, I believe, might benefit from a more extensive discussion.

She shows that the term "sub-lethal damage" is appropriate to the familiar multi-target model (model 1) in which the fraction, $S(D)$, of cells surviving a single acute absorbed dose D, is given by:

$$S(D) = 1 - \{1 - \exp(-\lambda D)\}^n \quad \ldots\ldots\ldots(1)$$

This model postulates that n vulnerable targets, each with the same inactivation constant, λ, all need to receive at least one radiation "hit" if the cell is to lose proliferative capacity. Equal weight and status is given to each of the n targets.

The term "potentially lethal lesion" is obviously appropriate to a repair model. Suppose that some lesions are irreparable, while others tend to be repaired before the next cell division after irradiation at low, but not at high, dose. Then the following equation modified from Haynes (1966) describes survival from a single acute irradiation for a simple "repair" model (model 2)

$$S(D) = \exp\left[-k_i D - k_r D\{1 - \exp(-aD)\}\right] \quad \ldots.(2)$$

This model postulates a minimum of two qualitatively distinctive types of inactivating lesion, the irreparable type (which might be a heterogeneous category) represented by the $k_i D$ term; and the potentially lethal, potentially reparable lesion (which might also be heterogeneous) represented for convenience by the single term, $k_r D\{1 - \exp(-aD)\}$. At low D, with $aD \ll 1$, this "repair term" tends to $ak_r D^2$ and hence to zero as $D \rightarrow 0$; at high D, the term tends to $k_r D$. Furthermore, the term $\{1 - \exp(-aD)\}$ represents a third type of lesion—one that *interferes* with the repair of a potentially lethal lesion. Interference is negligible as $D \rightarrow 0$ but complete when aD becomes appreciably greater than unity and $\{1 - \exp(-aD)\} \rightarrow 1$.

We must expect that equations (1) and (2), with specific values assigned to the parameters λ and n, and k_i, k_r and a, will apply only to a particular type of cell, in a particular phase, under specific conditions of culture and for a given quality and dose-rate of radiation. The question we have to ask is: does either model relate to radiobiology and particularly to the radiobiology of radiotherapy?

In principle, two types of experiments are critical for distinguishing between models 1 and 2. At low dose the slope of the curve of ln $S(D)$ versus D given by equation (1), with $n \geqslant 2$, tends to zero, but to $-k_i$ for equation (2). At a *dose rate* that is low enough to allow full recovery or repair to occur, the same outcome and the same slopes should be observed. Although it is difficult to reduce statistical errors sufficiently to determine the shape and slope of the survival curve at low D, the bulk of the evidence from experiments on mammalian cells exposed to low LET radiations at low dose, or at low dose-rate, favours equation (2) over equation (1). Taking account of the additional arguments given by Alper (1977) we have to conclude that model 1 probably has little or no relevance to mammalian cells.

Dr. Alper refers only briefly to another category of quantitative evidence that, in my view, is of great value to the further understanding of radiation action: the dependence of RBE on LET. A simple theory of this phenomenon (Burch, 1970a, b) fits a wide range of experimental findings and, in particular, offers a consistent interpretation of the results of Barendsen *et al.* (1966) for the inactivation of human cells of kidney origin. For irradiations under aerobic and anoxic conditions, and at "low" dose (survival from 1.0 to 0.5) and "high" dose (survival from 0.1 to 0.01), this theory identifies in each circumstance a minimum of three distinctive modes of radiation action.

At low LET (around L_∞ of 1 keV μm^{-1}), a "single energy transfer" mode of inactivation predominates, but as LET rises this mode becomes less important both absolutely and relative to the other modes of inactivation. The effective cross-section for this mode also varies widely with dose. Under aerobic conditions, the effective cross-section for inactivation at "low dose"—as defined above—is about $0.05(\mu m)^2$ per cell, rising to nearly $0.9(\mu m)^2$ at "high dose". Under anoxic conditions, the corresponding cross-sections are $0.01_6(\mu m)^2$ and $0.2_6(\mu m)^2$, respectively. A high degree of repair of this type of lesion under "low dose" conditions can be inferred; the mechanism of repair involves, presumably, Sinclair's (1973) *Q*-factor.

At higher LET, a mode of inactivation becomes important that entails two separate energy transfers from an ionizing particle to a characteristic type of complex target: the maximum RBE occurs at L_∞ just over 20 keV μm^{-1}. If the average energy per transfer is 80 eV then the average separation between successive inactivating transfers is about 38 Å. This mode of cellular inactivation is markedly oxygen-dependent, with an OER of about 2 in the "high dose" region and about 3 in the "low dose" region but the effective cross-section shows, within the limitations of the analysis, little or no change with dose. In other words, we can infer that little or no repair of this type of lesion takes place under the circumstances of the experiment by Barendsen *et al.* (1966).

At still higher LET a third mode of inactivation predominates, giving a maximum RBE at L_∞ just over 100 keV μm^{-1}. This mode entails three separate transfers of energy from an ionizing particle to a characteristic type of complex target. If the average energy per transfer is 80 eV then the average separation between successive inactivating transfers is about 8 Å. The effective cross-section shows a suggestion of oxygen dependence (possibly 10% *higher* under anoxic conditions) but no indication of dose-dependence. This type of lesion, caused by a triple energy transfer, appears to be irreparable.

For each of these three modes of inactivation the "target" may be regarded as composite, comprising, for example, a very large number of vulnerable sections of nuclear DNA. For a more detailed discussion of the nature of this and the other lesions see Burch (1970a, b).

To decide whether "*P*-type" lesions (Alper, 1977) correspond to any of those described above it would be necessary to study their dependence on LET.

In conclusion, the analysis of the relation of RBE to LET strongly supports a "repair" model and the concepts of "potentially lethal, potentially reparable" and "irreparable" lesions. However, both categories of lesion are probably heterogeneous and their relative importance evidently depends on many factors.

Yours, etc.,
P. R. J. BURCH.

Department of Medical Physics,
University of Leeds,
The General Infirmary,
Leeds LS1 3EX.

REFERENCES

ALPER, T., 1977. Elkind recovery and "sub-lethal" damage: a misleading association? *British Journal of Radiology*, *50*, 459–467.

BARENDSEN, G. W., KOOT, C. J., VAN KERSEN, G. R., BEWLEY, D. K., FIELD, S. B., and PARNELL, C. H., 1966. The effect of oxygen on impairment of the proliferative capacity of human cells in culture by ionizing radiations of different LET. *International Journal of Radiation Biology* *10*, 317–327.

BURCH, P. R. J., 1970a. Track structure in relation to target structure. In *Second Symposium on Microdosimetry*, EUR 4452d-f-e, Editor H. G. Ebert, pp. 685–708, Commission of the European Communities, Brussels.

1970b. Stochastic equations relating RBE to LET. In *Charged Particle Tracks in Solids and Liquids*. Proceedings of the Second L. H. Gray Conference. Editors G. E. Adams, D. K. Bewley and J. W. Boag, pp. 127–139, Institute of Physics, London.

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SINCLAIR, W. K., 1973. N-Ethylmaleimide and the cyclic response to X rays of synchronous Chinese hamster cells. *Radiation Research*, *55*, 41–57.

(*in reply*)

THE EDITOR—SIR,

ELKIND RECOVERY AND "SUB-LETHAL DAMAGE": A MISLEADING ASSOCIATION?

The purpose of my contribution (Alper, 1977) was to draw attention to the lack of evidence supporting either of the basically different assumptions underlying two groups of models for cell-killing which I called the "multi-sub-lethal lesion" and "repair" groups.

Model 1 of Dr. Burch's letter is, of course, only one of the former group. As he says, there are many experimental observations that call into question the validity of that particular model, according to which a survival curve should have zero slope at zero dose. If this were a test for the "multi-sub-lethal lesion" concept in general, a decision would be easy; but there are several models—for example, to use Burch's notation, $\ln S\ (D) = -(\alpha D + \beta D^2)$ (Kellerer and Rossi, 1972)—that can easily accommodate experimental observations on effects of radiation given in fractions or at low dose rates.

Dr. Burch refers to evidence that might be derived from dependance of RBE on LET. With respect to quality of radiation, the choice between the groups of models seems to me to depend on success in predicting changes in initial slopes and "shoulder widths" of cell survival curves, rather than "RBE" effects in general. The validation of a repair model as a description of a survival curve would require *evidence* that some, but not necessarily all, potentially lethal lesions become less reparable by biochemical means as the LET of the radiation increases. It may be inferred, from certain radiobiological observations, that some potentially lethal lesions can be biochemically repaired, but no recognized repair mechanism has been conclusively shown to be related to a reduction in cell killing by ionizing radiation. Until the operation of intracellular biochemical repair is better understood there seems little hope of getting experimental evidence to relate reparability with quality of radiation.

Yours, etc.,
TIKVAH ALPER.

Gray Laboratory,
Mount Vernon Hospital,
Northwood, Middlesex HA6 2RN.

REFERENCES

ALPER, T., 1977. Elkind recovery and "sub-lethal damage": a misleading association? *British Journal of Radiology*, *50*, 459–467.

KELLERER, A. M., and ROSSI, H. H., 1972. The theory of dual radiation action. *Current Topics in Radiation Research Quarterly*, *8*, 85–158.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *B.I.R. BULLETIN* which is distributed quarterly to all members.

RECENT ADVANCES IN HYPERTHERMIA RESEARCH

A radiobiology meeting will be held on May 11–12, 1978 (not May 18 as announced earlier this year), at the British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Details and registration, contact the General Secretary, B.I.R. (01–935 6237).

B.I.R. CONVERSAZIONE

Will be held at Northwick Park Hospital, Middlesex on May 17, 1978. Dr. Louis Kreel will arrange demonstrations and give a talk "Introducing art into radiology".

Details from the General Secretary.

HIGH DOSE RATE AFTERLOADING GYNAECOLOGICAL IRRADIATION AS AN ADJUVANT TO GYNAECOLOGICAL SURGERY: AN ASSESSMENT OF THE CATHETRON

An evening meeting will be held on May 18, 1978 at The British Institute of Radiology (Reid-Knox Hall), 32 Welbeck Street, London W1M 7PG.

Further details from the General Secretary.

THE 22ND CROOKSHANK LECTURE

The 22nd Crookshank Lecture entitled "Advice to the Royal Commission on the Task as They See it" will be delivered by the Rt. Hon. Lord Robens of Woldingham, P.C., D.C.L., LL.D., D.Univ. at 66 Portland Place, London W1N 4AD at 4.30 p.m. on Friday May 19, 1978.

The Chair will be taken by the President of the Royal College of Radiologists, Professor R. E. Steiner.

The lecture will be preceded by an Admission of Fellows.

Admission is free to all members of the Medical Profession.

BENIGN BONE DISEASE—ROLE OF RADIOISOTOPE TECHNIQUES

A meeting to be held at the Middlesex Hospital Medical School on May 31, 1978, organized by the British Institute of Radiology, with the British Orthopaedic Association, is intended to provide a comprehensive review of the application of radionuclide techniques in the evaluation of metabolic bone disease, assessment of fractures, infections and benign bone tumours.

A provisional programme and registration form from the B.I.R. 32, Welbeck Street, London W1M 7PG.

WORKSHOP ON THE USE OF COMPUTERIZED TOMOGRAPHIC SCANNERS IN RADIOTHERAPY

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proferred papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

WORLD FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY

To be held September 17–21, 1978. The Second International Congress of the World Federation of Nuclear Medicine and Biology will provide an international forum for the exchange of scientific information, the dissemination of knowledge, and the world-wide promotion of the discipline of nuclear medicine.

The Scientific Symposia will encompass all the activities and interests of nuclear scientists and physicians: medical and health physics; instrumentation; data analysis; radiochemistry; radioassays; *in vivo* and *in vitro* biochemical and physiological measurements; radiopharmaceuticals; functions and disorders of the cerebral, pulmonary, cardiovascular, abdominal, renal,, peripheral vascular, bone, joint endocrine, and metabolic systems.

There will be three pre-meeting courses: cardiovascular nuclear medicine; positrons, cyclotrons, and tomography; nuclear medicine in developing countries. During the meeting, there will be review teaching sessions on the state of the art in clinical nuclear medicine.

The technologist programme will include considerations of quality assurance, recruitment, education and career opportunities.

The meeting has been designed to afford maximum opportunities for exchanges of ideas and views among nuclear colleagues.

Morning activities will provide a plenary session, time for small discussion groups, and for visiting the exhibits of equipment and radiopharmaceutical manufacturers.

Afternoons will be devoted to contributed papers, poster sessions, panels and mini-symposia.

Further information from Dr. H. N. Wagner, President, WFNMB Second International Congress, 1629 K Street, N.W., Suite 700, Washington, D.C., 20006, USA.

BRITISH MEDICAL ULTRASOUND SOCIETY ANNUAL MEETING AND EXHIBITION

Will be held November 27–28, 1978 at the Civic Centre, Newcastle Upon Tyne.

Further details from the British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

Book reviews

Radiopharmaceutical dosimetry symposium 327
Lymphoreticular disease 332
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Manuel de techniques radiographiques du crane 350
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Radiation protection design guidelines for 0.1–100 MeV particle accelerator facilities: NCRP report No. 51 369
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The adult postoperative chest 380
Practical atlas of cardiac scintigraphy 388
The physical principles of diagnostic radiology 391
Paleopathological diagnosis and interpretation 391

Book received

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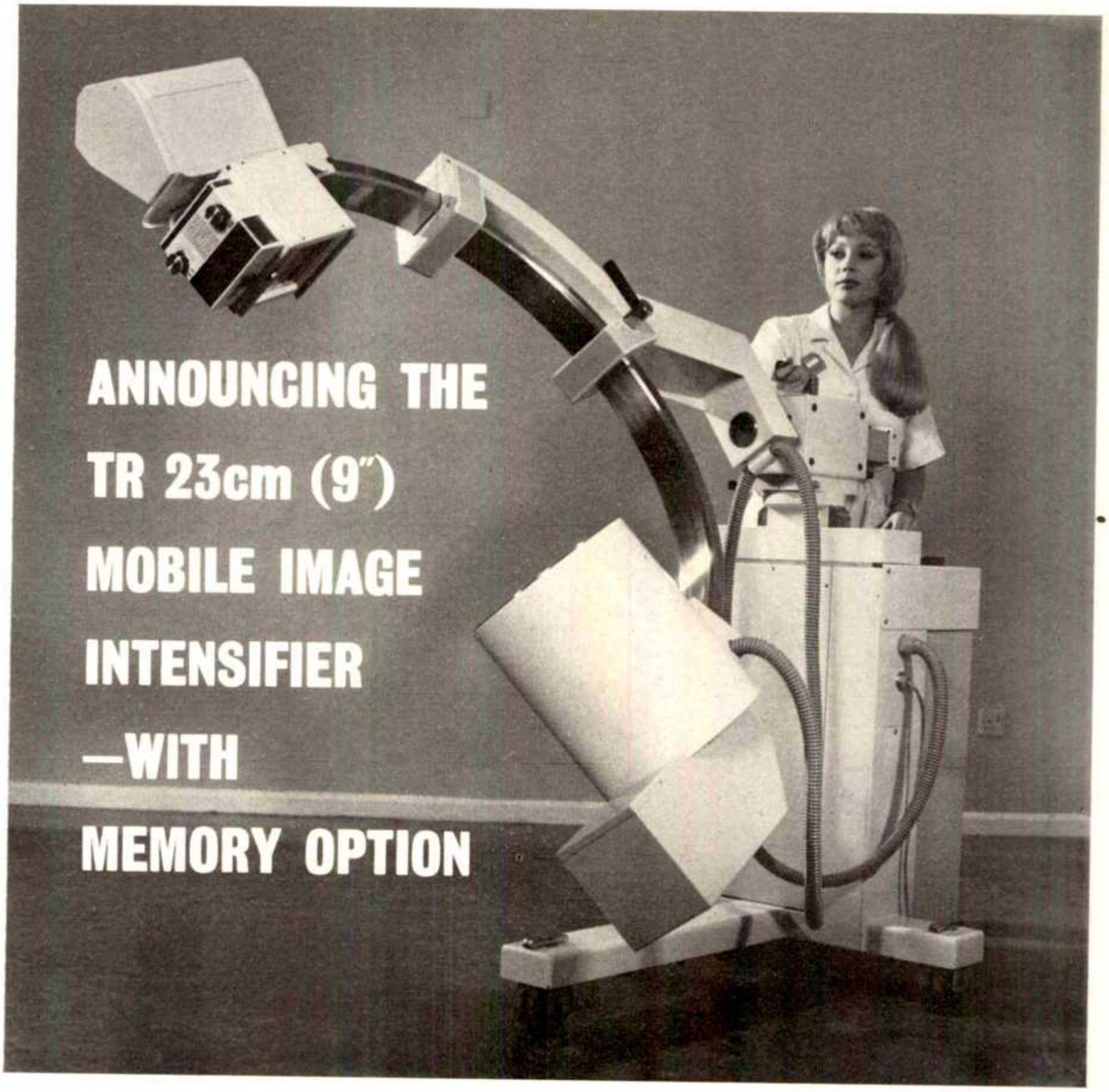

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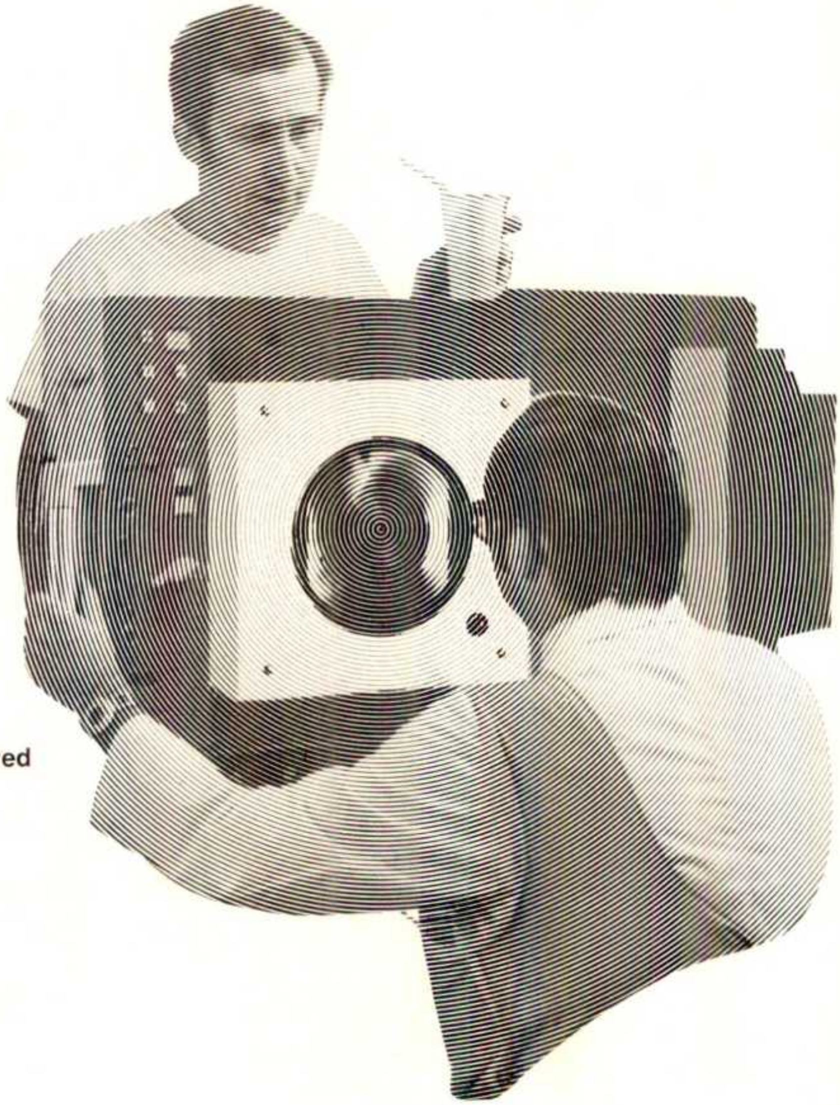

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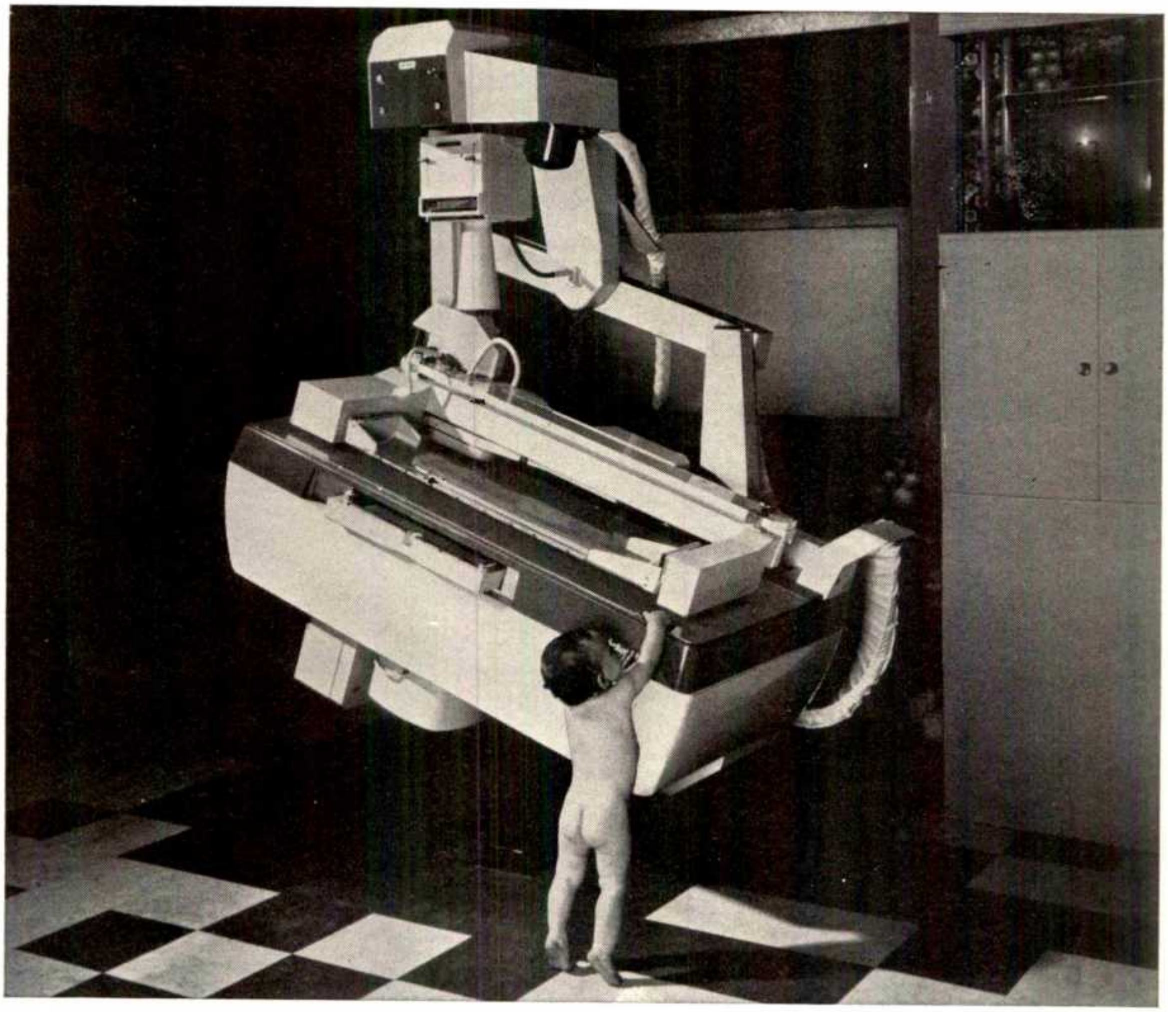

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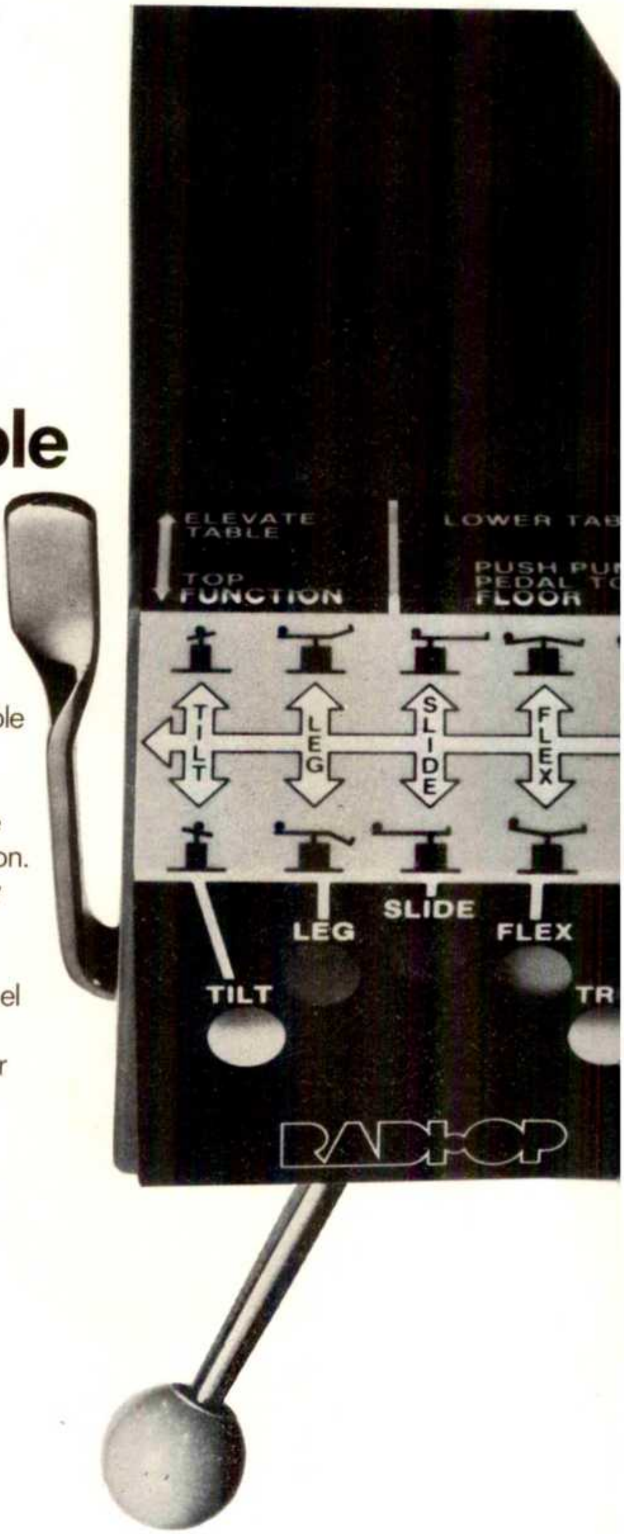

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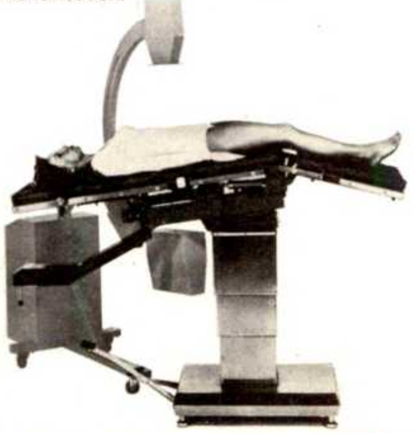

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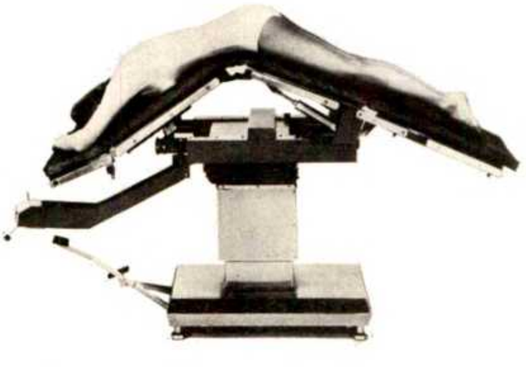

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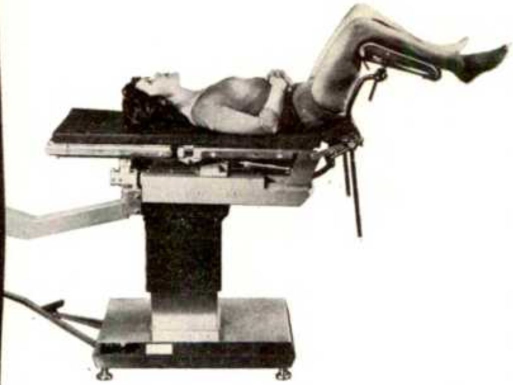

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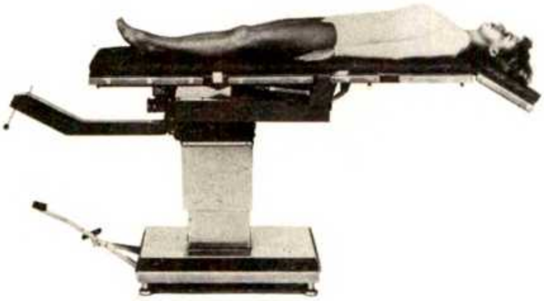

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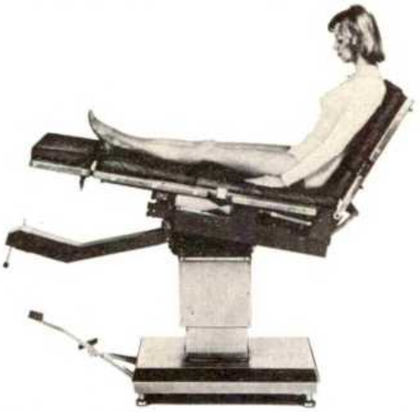

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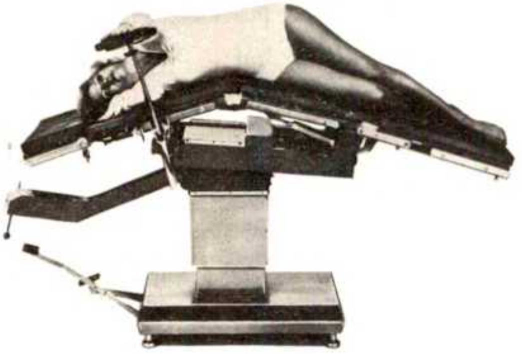

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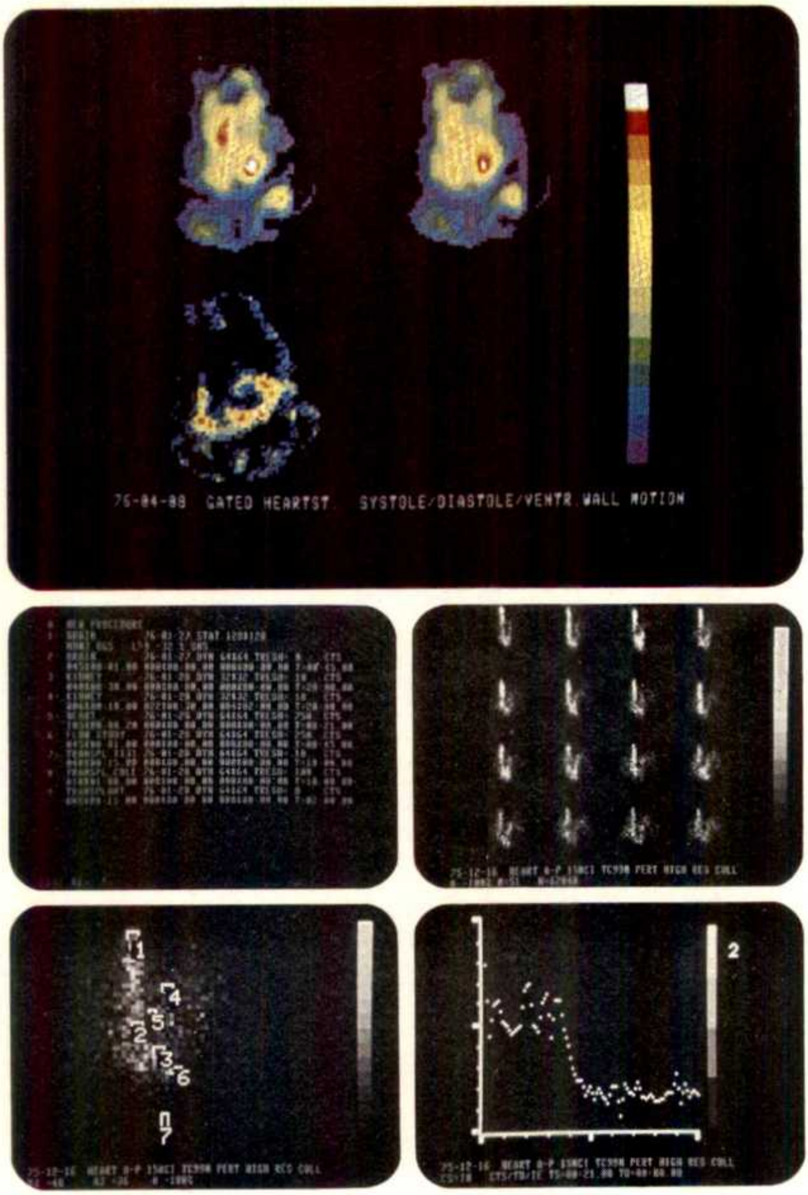

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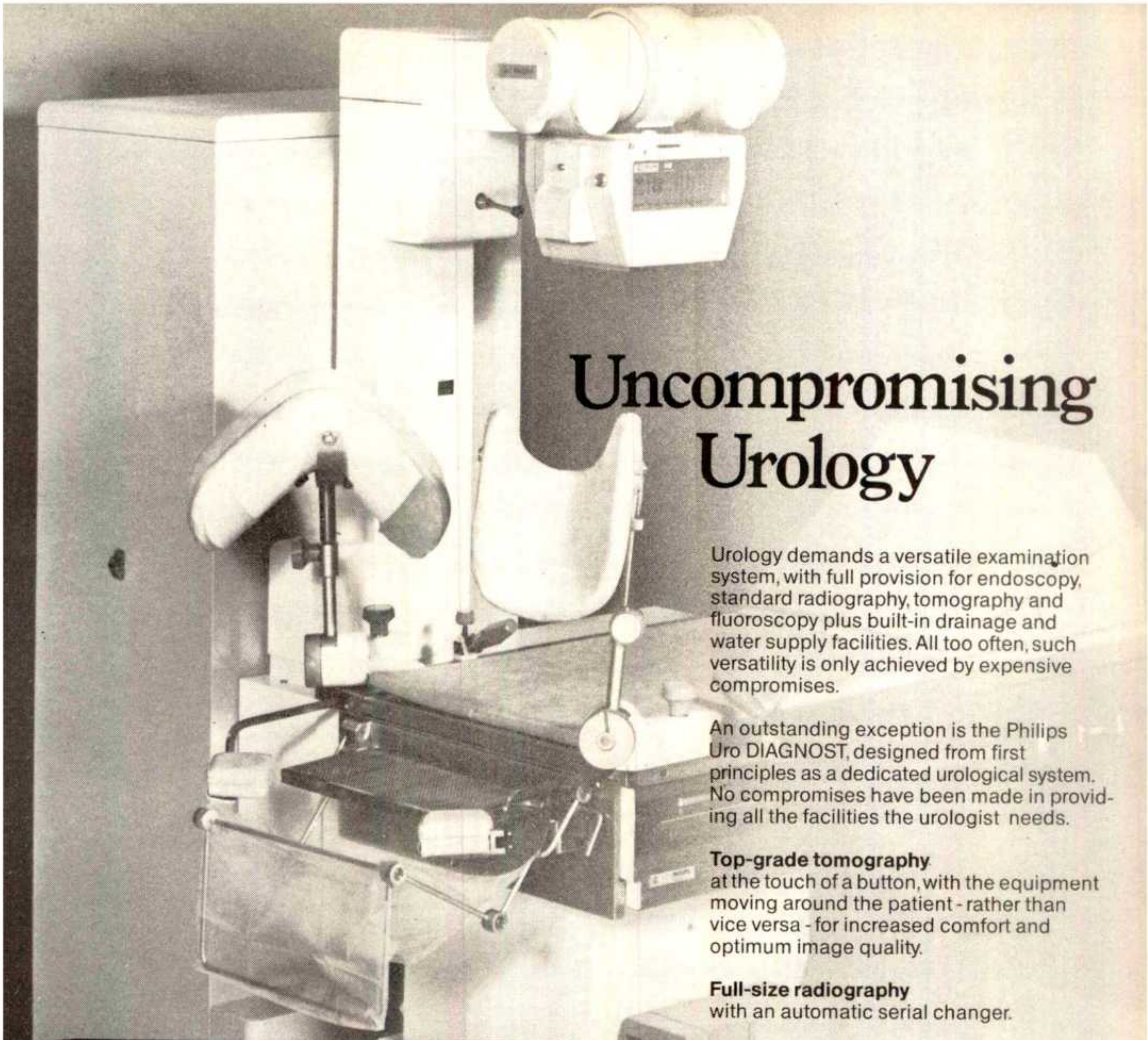

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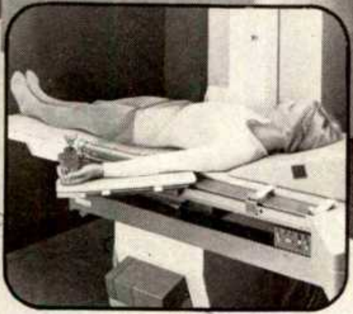

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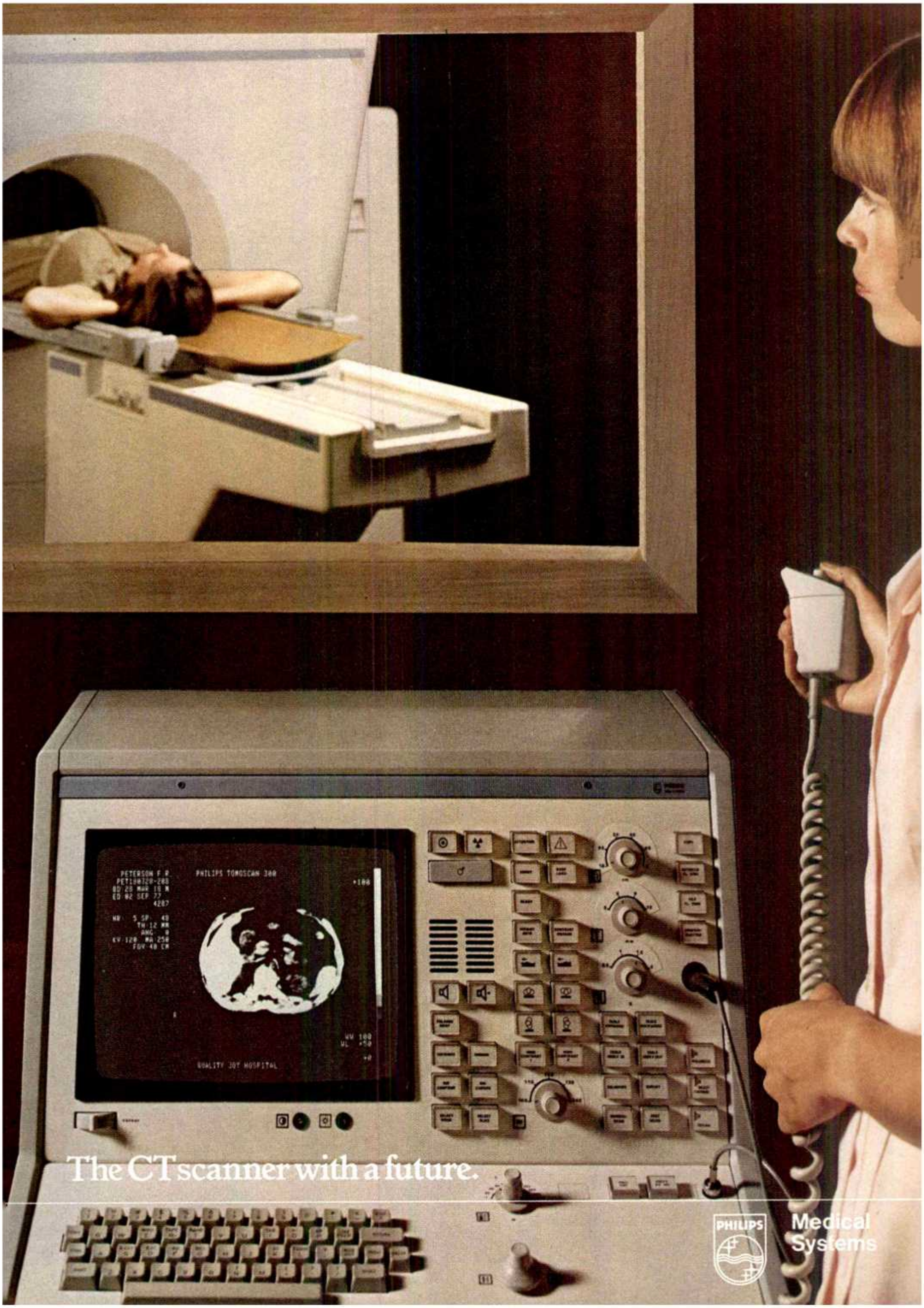
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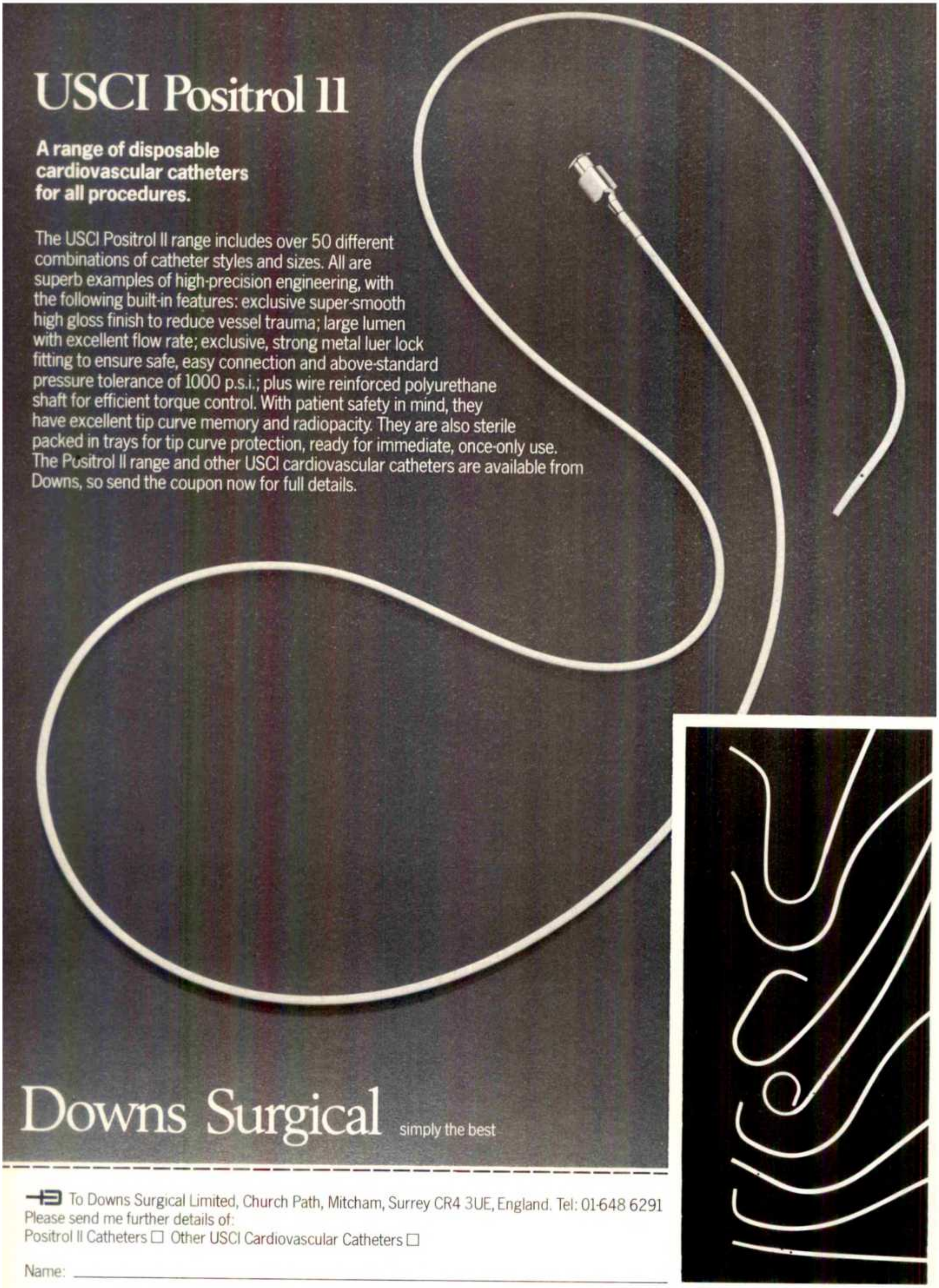

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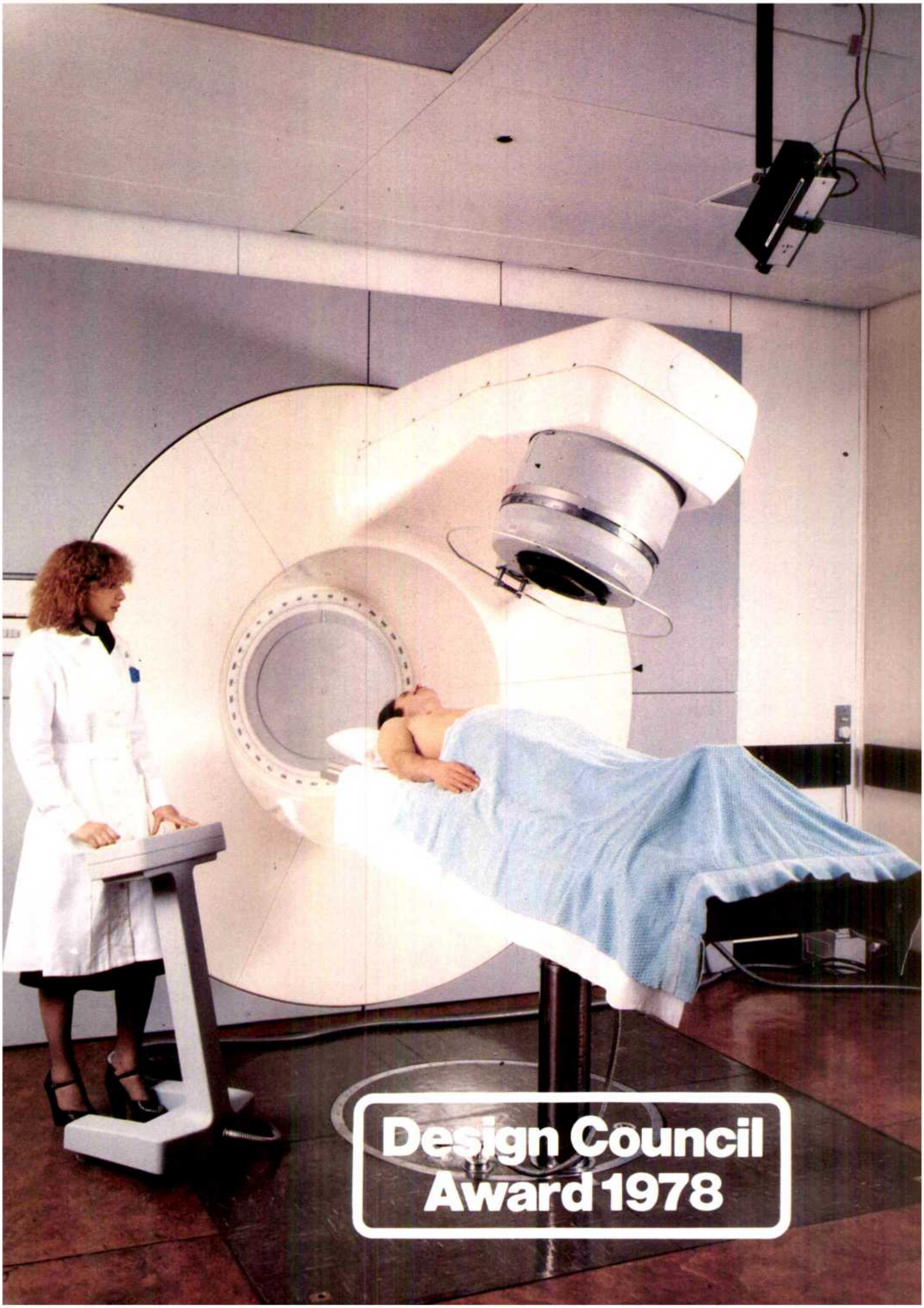
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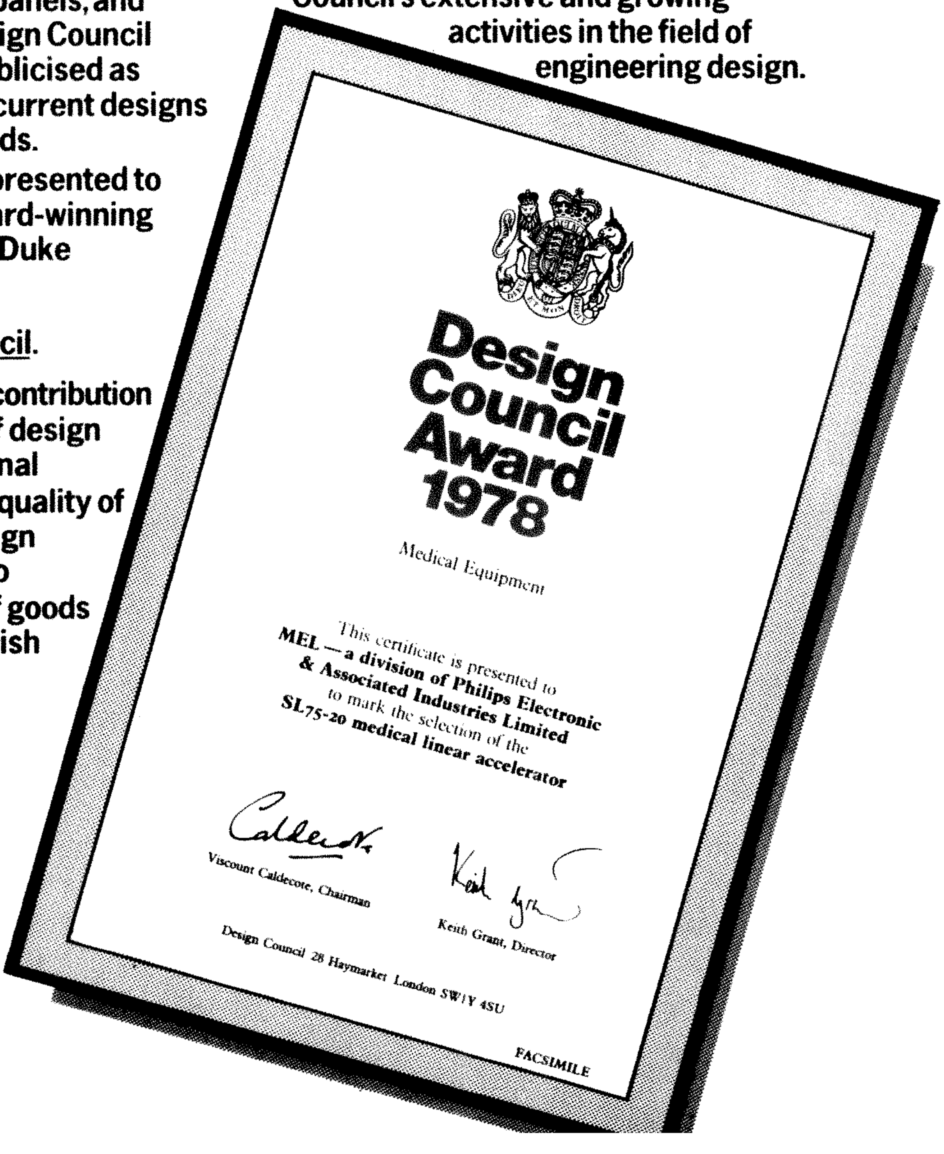

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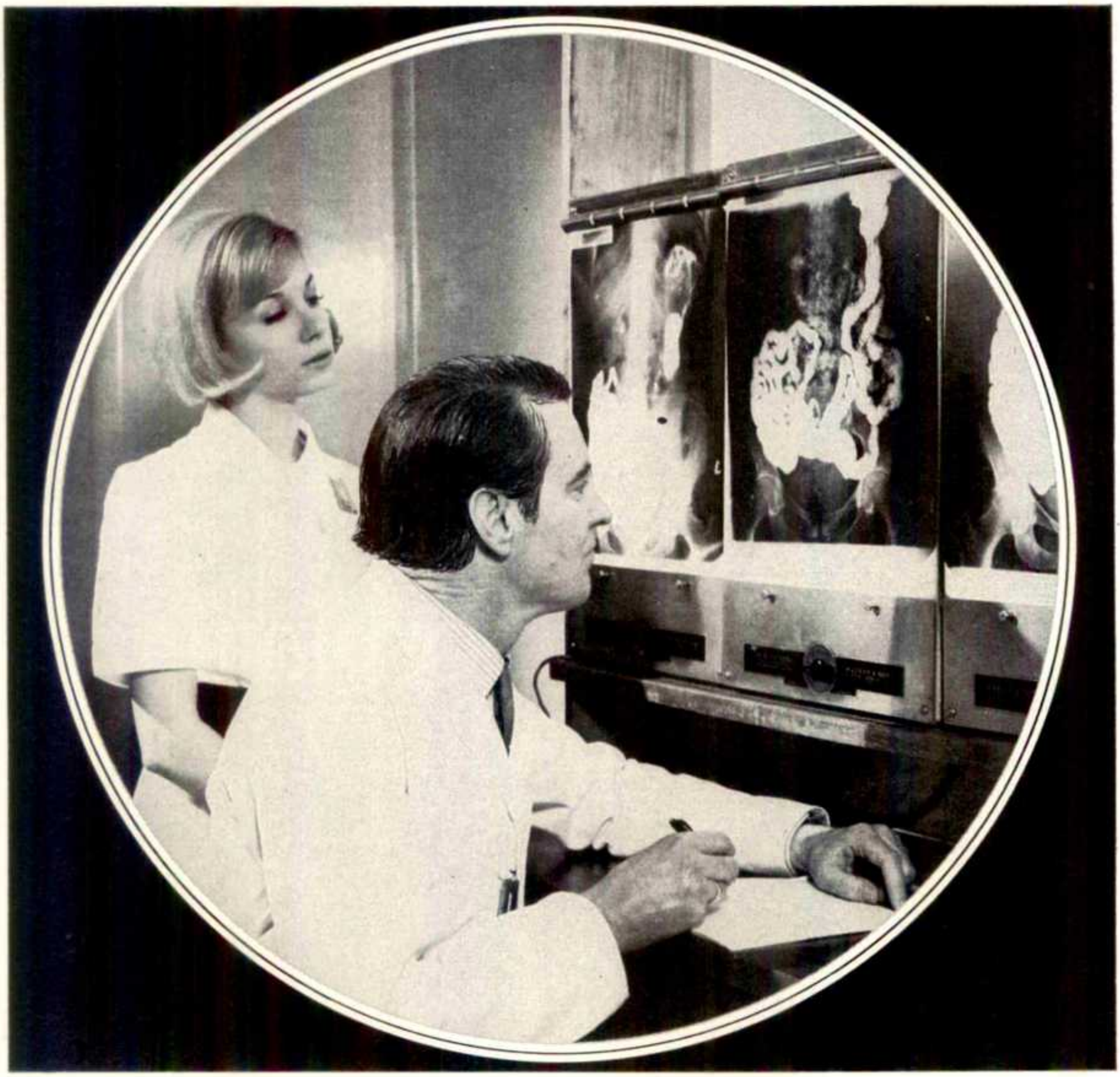

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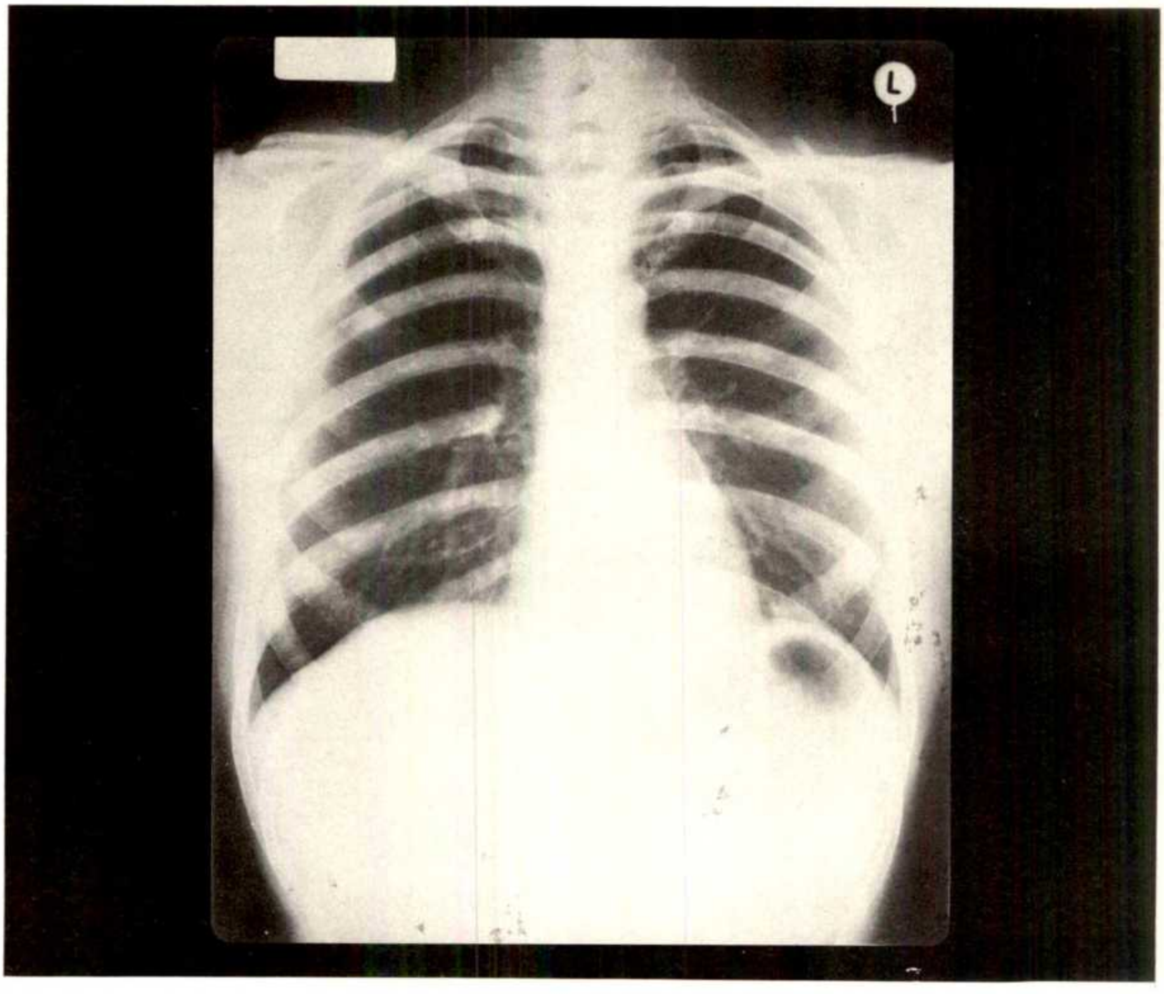

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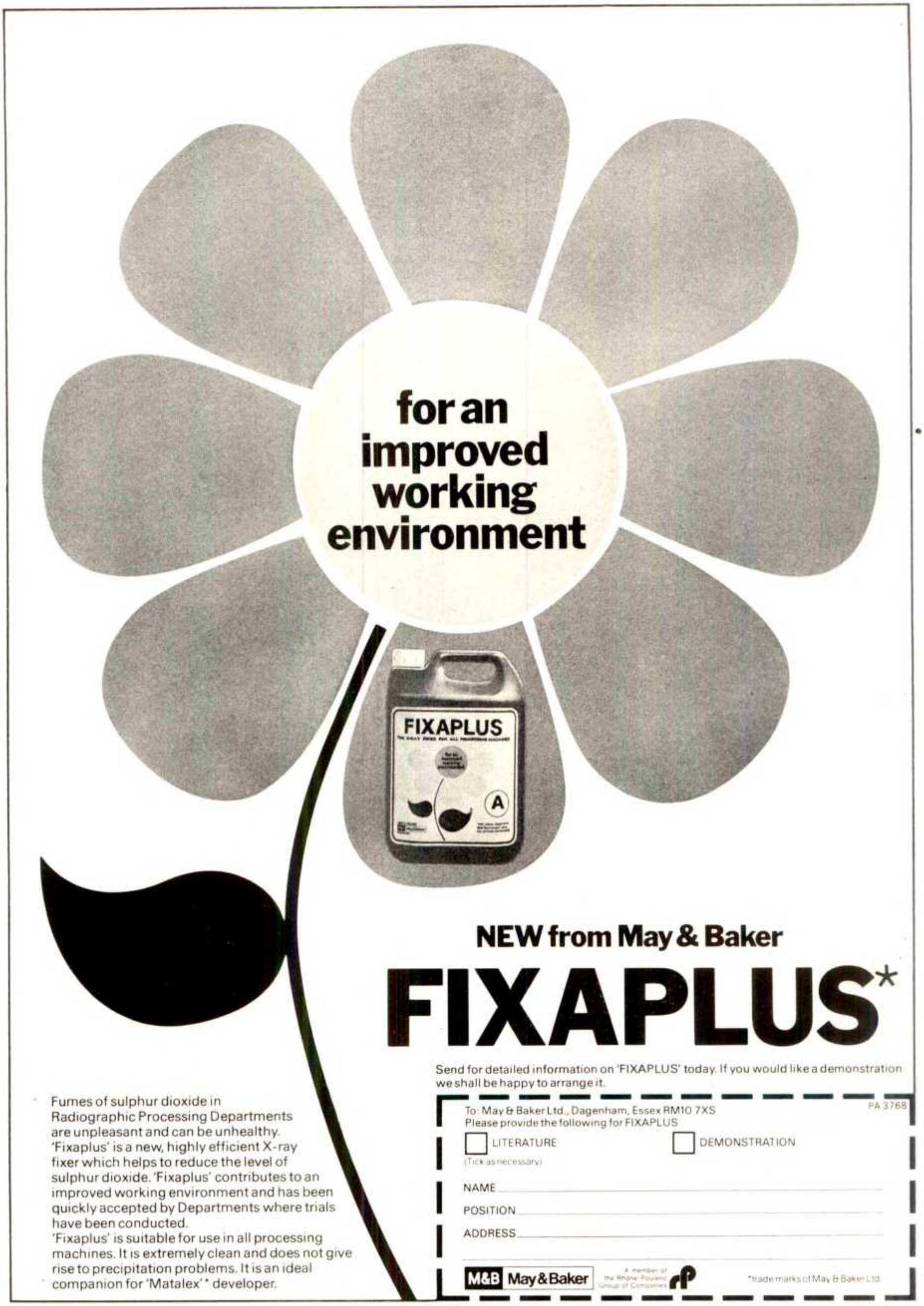

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1) *British Journal of Radiology* including *Archives* etc. from 1896 to present (five volumes missing).
2) *Clinical Radiology* complete from Vol. 1 to present.
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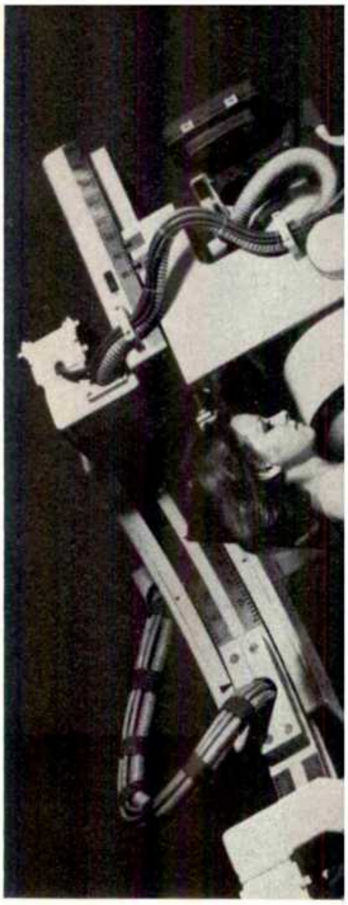

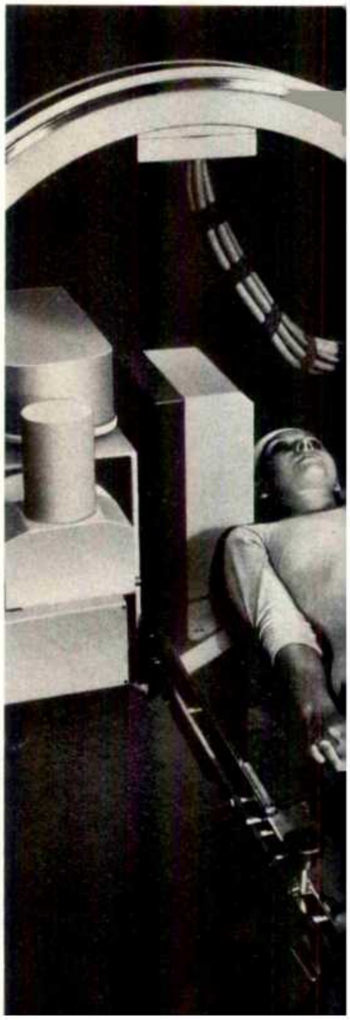

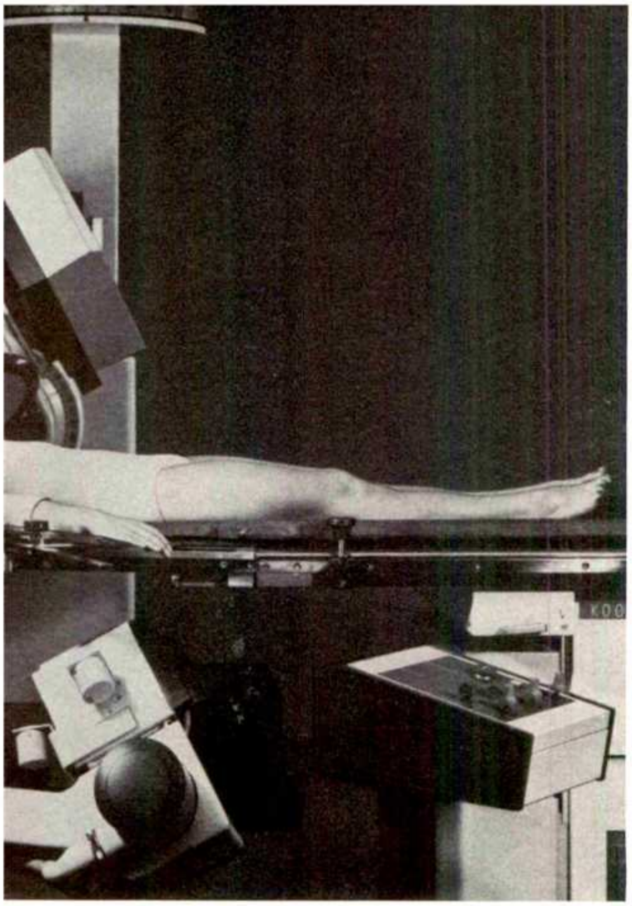

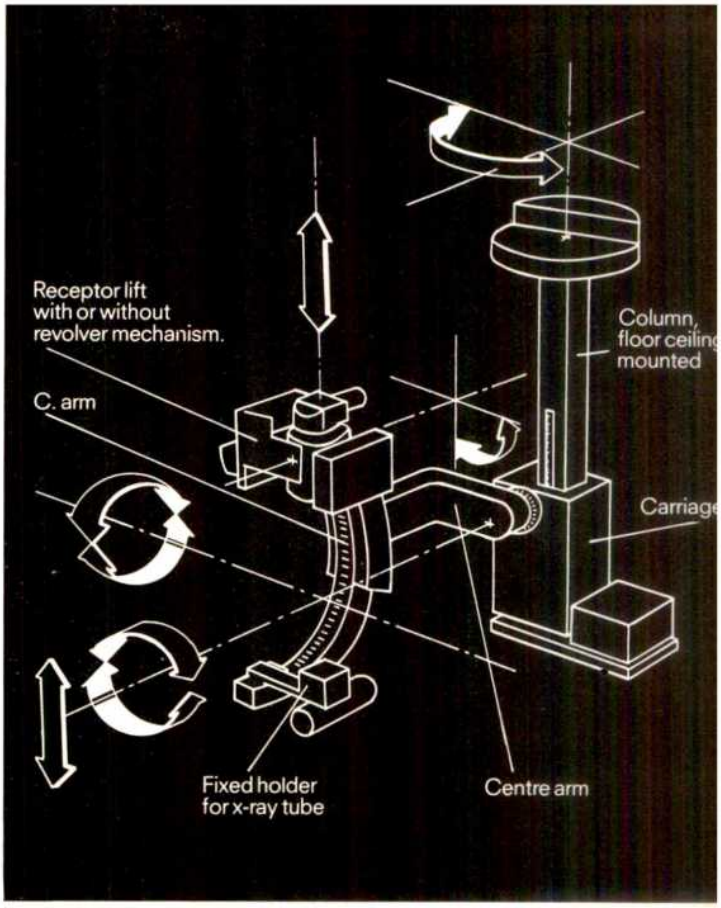
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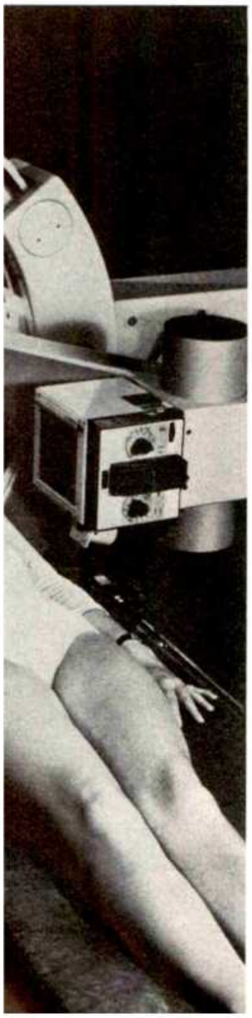

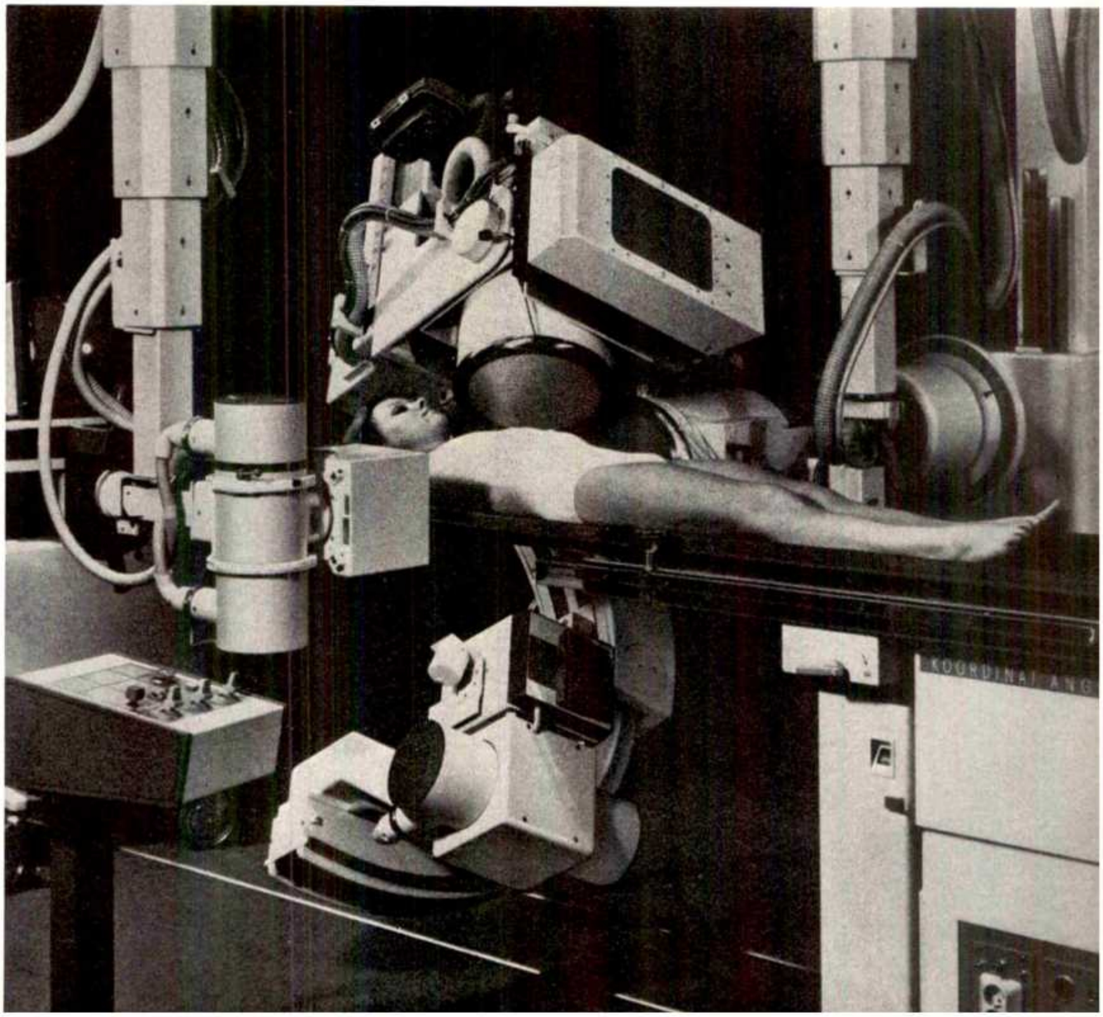
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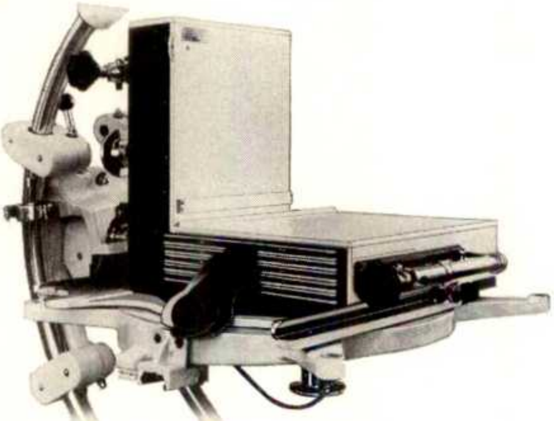

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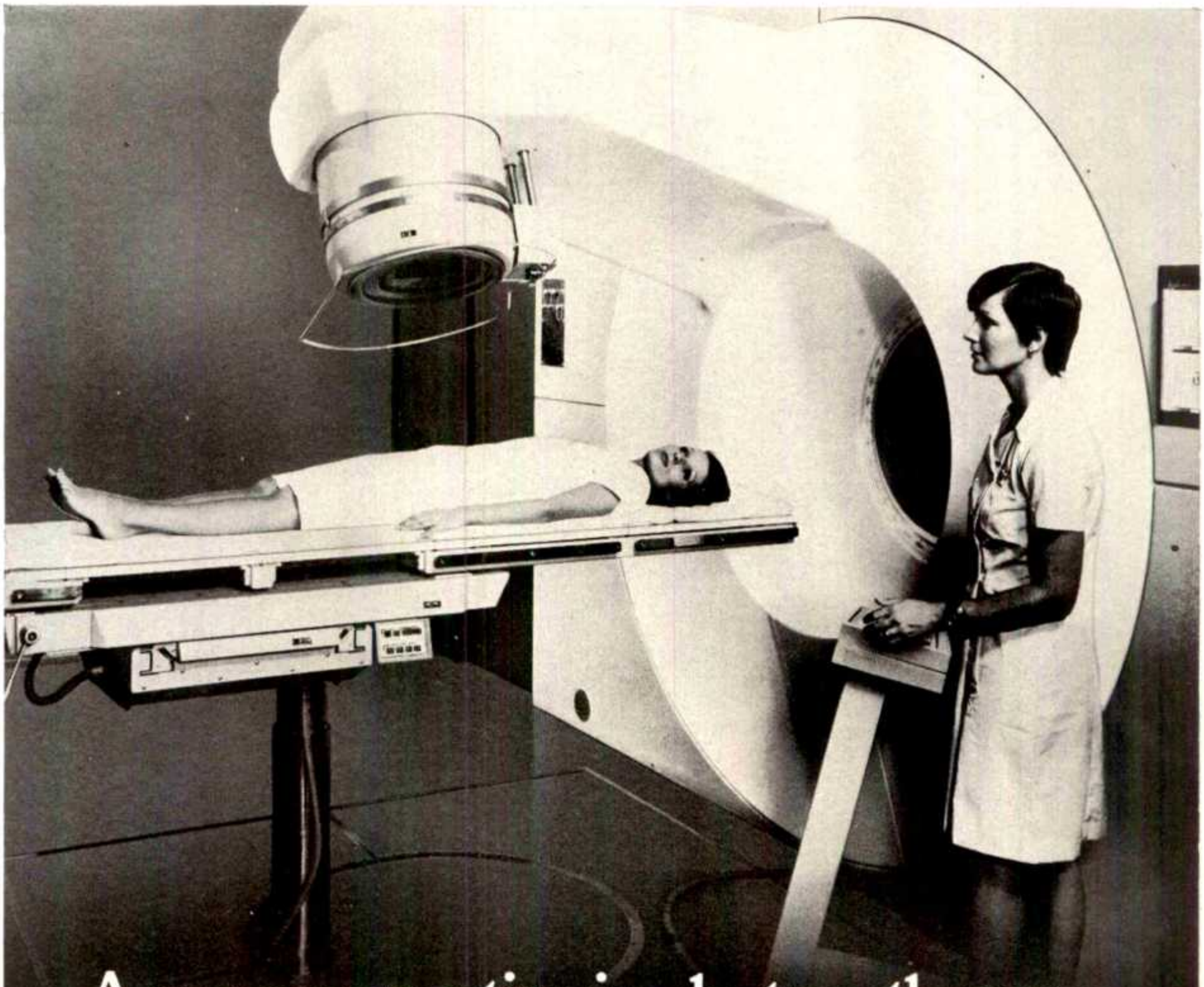

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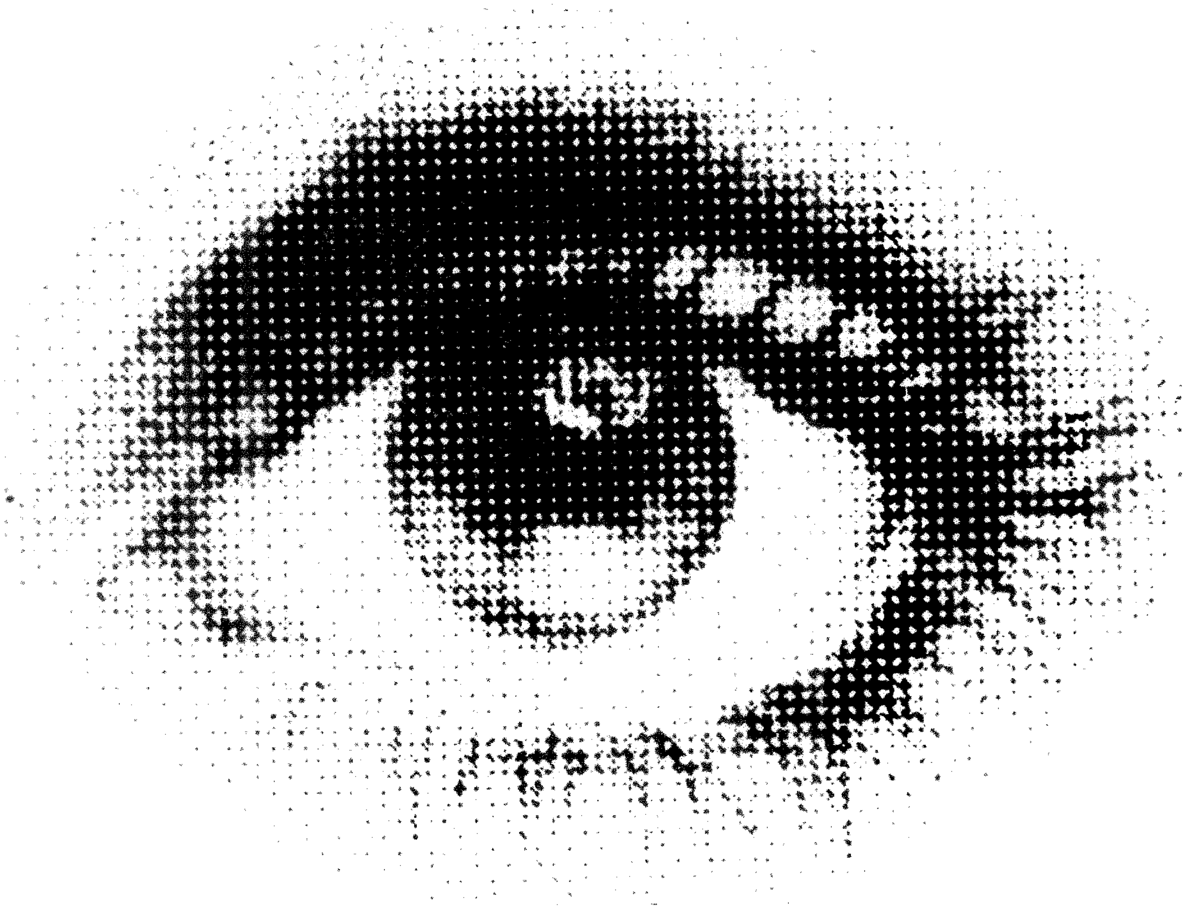

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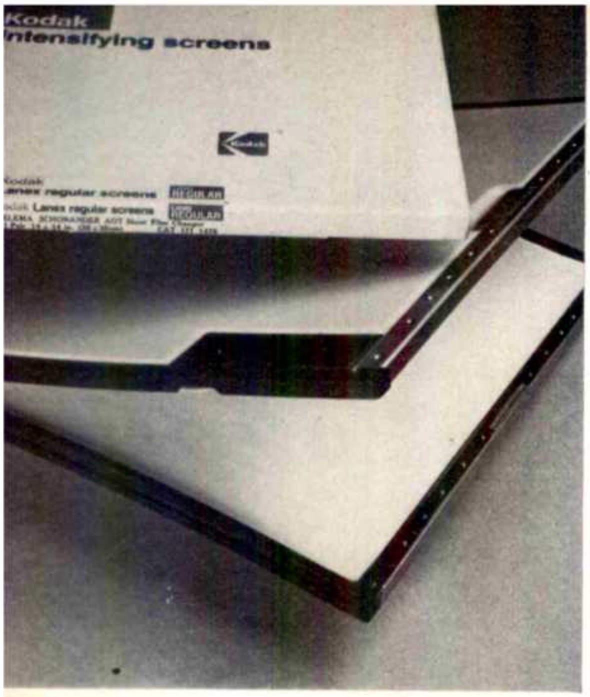

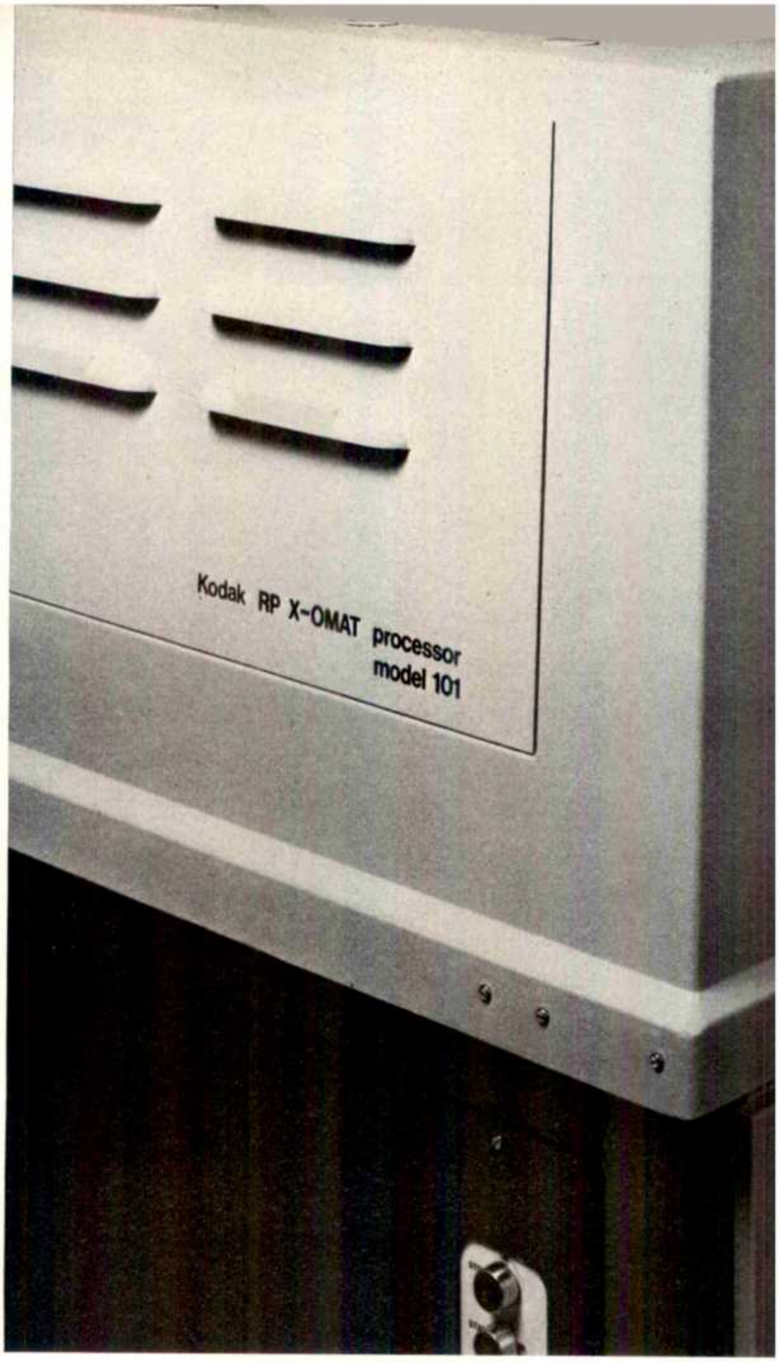

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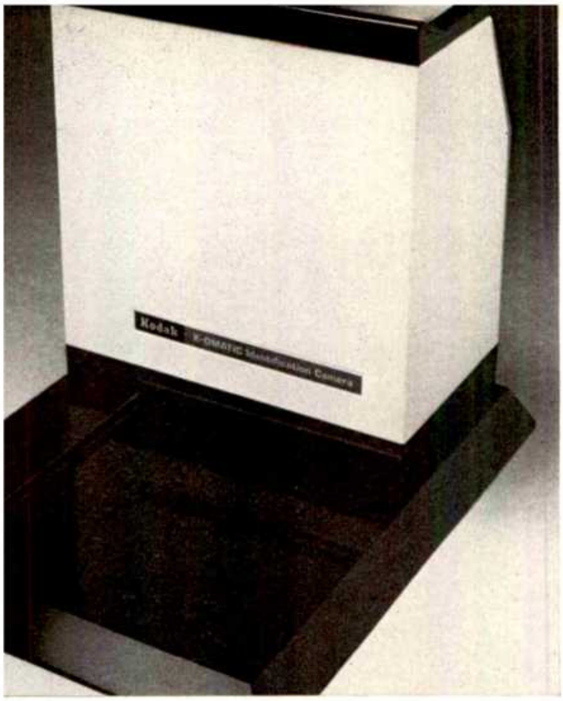

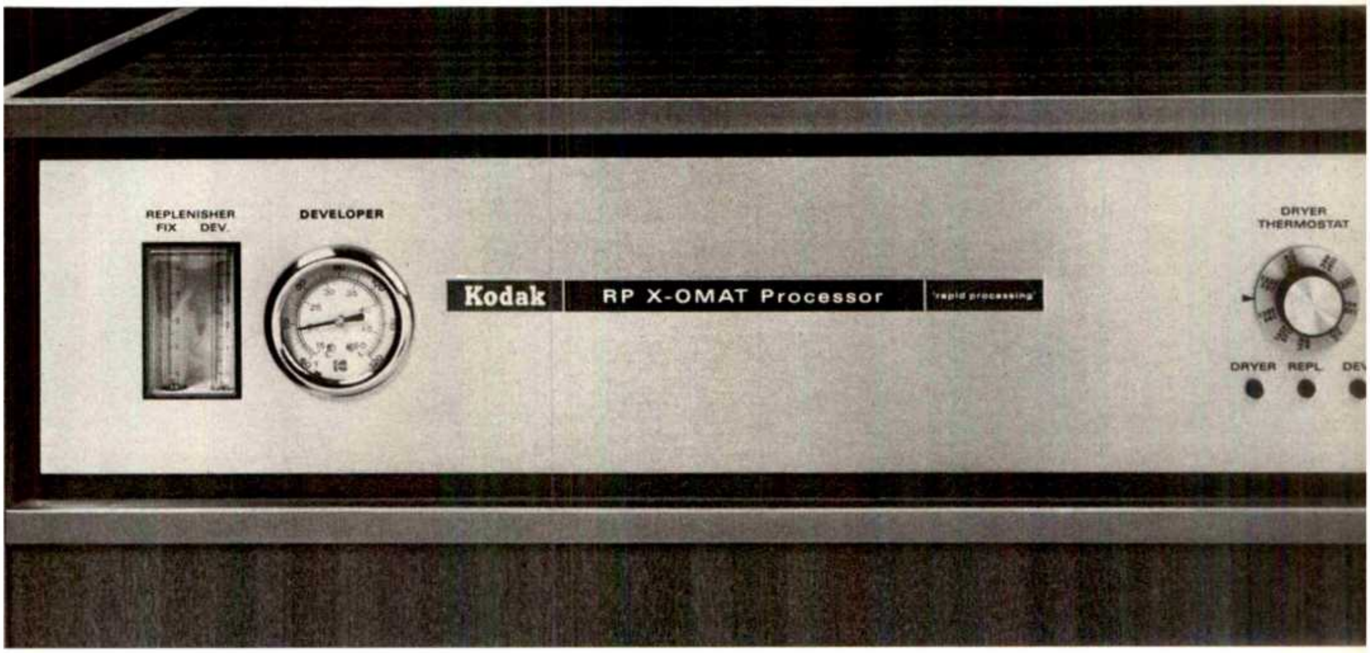

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The British Journal of Radiology

Review article

The sensitivity of the human breast to cancer induction by ionizing radiation

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(Received December, 1977 and in revised form February, 1978)

It is often difficult to accept that cancer induction by small doses of radiation is more than a theoretical possibility but actually happens. Indeed it is only quite recently that confirmatory evidence of considerable weight has become available to support the conclusion that the breast may be more sensitive to cancer induction by ionizing radiation than any other human tissue.

Evidence that Ionizing Radiation causes Breast Cancer in Humans

Multiple fluoroscopy as employed in the treatment of pulmonary tuberculosis by artificial pneumothorax

Two groups of female patients have been followed up for ten to 44 years (mean follow-up each exceeding 25 years) (in Nova Scotia by Myrden and Hiltz, 1969; BEIR, 1972, and in Massachusetts by Boice and Monson, 1977). In the first series breast cancer incidence was five times, in the other twice, what would be expected in controls (tuberculous patients treated without pneumothorax, or regional population statistics). Other series may fail to show an increase but this is to be expected given the numbers of subjects, the magnitude of the breast doses and/or the use of mortality instead of incidence as the index of effect.

In the two surveys mentioned there was an approximately linear relationship between excess breast cancer incidence and number of fluoroscopies. This is as would be predicted from the simple hypothesis that cancer frequency caused by multiple small doses of radiation would be proportional to total accumulated dose. Of course the dose for an individual fluoroscopic examination is impossible to determine with any accuracy so many years later even if the original equipment is available for calibration of output dose-rate (as it sometimes is): the duration of an individual fluoroscopy is an unknown variable. However, this does not alter the demonstration that breast cancer induction has been linearly proportional to number of fluoroscopies nor does it altogether falsify estimates of breast cancer risk per rad of tissue dose. These estimates have to be based on a decision about the average duration of a fluoroscopy as it was practised in particular institutions several decades ago and over a period of years and the risk estimates quoted below may thus be in error by a factor of perhaps 2 to 5, quite apart from statistical considerations, but they cannot be wholly wrong.

Radiotherapy of post-partum mastitis and other non-malignant diseases of the breast

The tissue doses here are known fairly exactly but, to set against this, the irradiated tissue was not normal and the individual treatment doses were ten to 100 times larger than for individual fluoroscopic examinations. The observations, therefore, cannot be so easily assumed to be relevant to occupational exposure or screening by mammography.

Radiotherapy of acute post-partum mastitis in New York led to a doubled increase in breast cancer incidence as compared with non-irradiated cases or sibling controls (Mettler *et al.*, 1969; Shore *et al.*, 1977). Radiotherapy of a variety of benign breast diseases in Stockholm with considerably larger total doses increased expected breast cancer incidence by four to six times (Baral *et al.*, 1977).

Japanese bomb survivors

By 1969 the incidence of breast cancer in those exposed to ten or more rad (kerma) was increased by

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TABLE I.

Breast cancer mortality in Japanese bomb survivors 1950–1972
(primary data in Tables 2 and 13.2–13.5 of Moriyama and Kato, 1973).

	Age at time of irradiation (years)		
	0–9	10–34	35+
Breast cancer deaths			
Number observed for all exposures of 10 rad (kerma) or more	0	21	20
Number expected:			
(a) from experience of those who received 0–9 rad,	0	6.4	19.3
(b) from Japanese national statistics.	very small	7.8	12.6
Excess rate per 100000 person-years in those who received 10 rad or more*			
Base-line (*a*)	0	8.8	0.7
Base-line (*b*)	0	7.9	7.2

*(i) Whether there is a striking difference in age-related sensitivity to breast cancer induction or not depends entirely on the choice of the control population. It so happens that bomb survivors receiving 0–9 rad at age 35+ years suffered 41 breast cancer deaths in 1950–1972 as compared with an expectation of 26.9 as judged by Japanese national statistics. This difference is too great to be attributed to the mean radiation dose received by the 0–9 rad group. It may be attributed to chance, in which case the national statistics would provide the appropriate base-line for risk evaluation, or to some systematic difference between the bomb survivor population and the generality of Japanese (which seems very likely), in which case the 0–9 rad group of survivors would provide the better base-line.
(ii) McGregor *et al.* (1977, Table 3) used base-line (*a*) when comparing frequencies of breast cancer diagnoses. The excess rates per 100000 person-years were 0, 18.8 and 7.8 for the three age-groups respectively for the period 1950–69. The ratio between the rates for those irradiated at 10–34 years and 35+ years was smaller for diagnoses than for mortality by about 1:4. McGregor *et al.* (1977) noted that the main contribution of new cases after 1960 was from the 10–34 year age group and also that ascertainment for diagnoses in 1965–69 was likely to be incomplete.

a factor of 1.5 to 2 over those receiving 0–9 rad (McGregor *et al.*, 1977). By 1972 mortality from breast cancer was also one and a half times to twice that expected (UNSCEAR 1977) and was largely confined to those irradiated when less than 35 years of age (Table I) The incidence of breast cancer per rad was closely similar at Hiroshima and Nagasaki, for deaths (Mole, 1975) and for diagnoses (McGregor *et al.*, 1977), showing that the RBE of fission neutrons cannot much exceed one for induction of breast cancer in women.

The full reports of four of these surveys have just been published and substantial citations from all of them can be found in two very recent reviews (Upton *et al.*, 1977; UNSCEAR 1977). The results discussed below are extracted from one or other of these unless specifically referenced.

Application of this Evidence to Practical Problems

The mean absorbed dose to breast tissue for an individual fluoroscopic examination was inferred to be 7.5 or 3.6 rad in the Nova Scotia series, depending on the method of assessment, and 1.5 rad in the Massachusetts series. At levels of dose from 10 rad of low LET radiation downwards there is no known radiobiological reason for expecting much variation in frequency of effect per rad according to the magnitude of an individual exposure or according to the number of successive, spaced exposures. It is perhaps remarkable, given all the other problems of analysis, that the overall risk estimate per rad is so similar in the two fluoroscopy series (Table II). It is further remarkable that the risk estimates for the two radiotherapy series agree so well with each other and with the fluoroscopy series (Table II).

These estimates are primarily for young adult women and, although many fewer older women were serially fluoroscoped, the evidence (Table II) may suggest quite strongly that older women are less sensitive. However, the risk estimate for incidence in Japanese bomb survivors appears not to be strikingly greater for young than for older adults (in contrast with mortality, see Table I). Upton *et al.* (1977) cited an unpublished report of an increase in second breast cancers in women given radiotherapy for a first breast cancer with a risk estimate comparable to those for the other series: if all the second cancers are attributable to the dose received by the irradiated breast it might appear that older women cannot be strikingly less radiosensitive than younger women. However, it seems clear from the Massachusetts fluoroscopy series and the Japanese bomb survivors (both for incidence up to 1969 and mortality up to 1972) that the maximum sensitivity to breast cancer induction by radiation is in women at some period between 10 and 20 years of age. There are case reports of breast cancer following doses exceeding 100 rad in the age range 0 to 10 years but the epidemiological evidence is that sensitivity is much less before puberty than afterwards. It is certainly an attractive working hypothesis to postulate that the sensitivity of the human breast to cancer induction by ionizing radiation is correlated with hormonally regulated tissue activity.

The risk estimate for induced breast cancer frequency in Japanese bomb survivors is lower than any other value in Table II and some of the difference, but not all, is removed by allowing for the much

TABLE II.

Risk estimates of induction of human breast cancer by ionizing radiation when both breasts are exposed.

	Frequency of breast cancer in excess of controls			Notes on information relevant to variation in radiosensitivity with age at exposure*	
	per million subjects per rad mean breast dose		years of follow-up		
	UNSCEAR 1977	Upton *et al.*, 1977†	range in years		
Fluoroscopy					
Nova Scotia	30–140 ("perhaps greater")	150‡	10–28	20 cases in excess in 234 subjects up to 29 years old	No breast cancers in 66 subjects aged 30 years and more
Massachusetts	113	210	10–44 (mean 27)	18 cases in excess in 804 subjects up to 29 years old	No excess cases in 243 subjects aged 30 years and more
Radiotherapy					
Acute post-partum mastitis (New York)	—	200	10–34 (mean 25)	20 cases in excess in 560 subjects up to 40 years old	
Benign breast disease (Stockholm)	175	—	6–42 (mean 32)	About 100 cases in excess in 1115 subjects. Excess most pronounced in those under age 35 when irradiated.	
Atom bomb survivors					
Japan	—	60§	5–24	About 33 cases in excess (all ages known doses). Excess rate at 35 + years perhaps 1/4–1/2 of rate in young adults	

*The number of cases in excess of expected depends on the control population used for the comparison and, since more than one control population was examined in several of the surveys, the excess noted may be an approximate figure.

†Upton *et al.* reported risks in terms of cases per million per year per rad. These annual rates have been converted to total risks by multiplying by the duration of follow-up as given and recorded above.

‡320 if mean breast dose = 3.6 rad, not 7.5 rad.

§Excluding subjects irradiated at < 10 years. The risk estimate given by Upton *et al.* was in terms of exposure. The value given above includes an approximate allowance for mean dose in breast tissue which is smaller than kerma.

higher proportion of older women amongst them than among those fluoroscoped or treated for acute post-partum mastitis (who in the nature of the case can rarely be more than 40 years' old when irradiated). Additional factors could be the normally lower natural breast cancer incidence in Japan than in occidental countries or the fact that the Japanese received single exposures all exceeding 10 rad (by definition, cf Table I) and running up to several hundred rad. The observed excess rate per rad appears to be smaller at the large doses both for incidence and mortality (though not significantly so in a statistical sense). Radiobiological reasons for expecting such a phenomenon have been discussed (Mole, 1975) and, if accepted, would bring the Japanese rate for single small exposures to a value quite close to the others in Table II. But, whatever the factors affecting the value of the mean risk estimate in Japanese bomb survivors, the weight of the other evidence seems inescapably to lead to the conclusion that the two adult human breasts are between them several times more sensitive to cancer induction than is human bone marrow. Risk estimates per rad of tissue dose for human leukaemia as commonly given rarely exceed one-quarter of the values for breast cancer given in Table II. An estimate of 15–25 cases per million per rad for low LET radiation at low dose is given by UNSCEAR (1977) and twice that by Mole (1977).

The minimum latent period before any induced breast cancer was seen was 10–15 years for fluoroscopy and radiotherapy but perhaps shorter in Japanese bomb survivors. The observations show that induced cases continue to appear for up to 40 years at least after exposure.

Mammography

Any risk of inducing breast cancer by mammography must be definitely smaller than the expected benefit if screening of well women by mammography is to be used on a population scale (Bailar, 1977). There seem to be two reasons for limiting such screening to women of 50 years and over. In the United States HIP trial of the value of mammmography in the early diagnosis of breast cancer (Shapiro, 1977) there has so far been no benefit for those under the age of 50. Secondly, the risk of mammography seems likely to be smaller at older ages because the natural expectation of life is then becoming shorter than the latent period for a proportion of the induced cancers and, in addition, the risk per rad of breast tissue dose may be smaller than for younger women. Further analysis of the Stockholm radiotherapy series and of data from the Japanese bomb survivors (see footnote Table I) may allow firmer conclusions about this latter question.

Other diagnostic radiology

If the Adrian Committee in 1956 had known what is known now about the radiation sensitivity of the human breast, it seems highly probable that it would have sponsored estimates of population breast dose from routine diagnostic radiology as well as estimates of bone marrow dose. Even without this information it may seem unlikely that medical radiology contributes significantly to the total of naturally occurring breast cancer.

Occupational exposure and radiological protection

Because of the growing evidence about the sensitivity of the human breast to cancer induction by ionizing radiation the recently revised (1977) Recommendations of the International Commission on Radiological Protection (Publication 26) have made exposure of breast tissue more restrictive than exposure of bone marrow. It may be noted that ICRP (1977) cited for protection purposes a single compromise value for the sensitivity of the human breast to be applied regardless of sex and age. Males are much less sensitive than females and the evidence for a progressive decrease in sensitivity of females from young adulthood to middle and old age has been alluded to. The ICRP compromise is appropriate for practical application because its dose limits are limits on annual dose and the associated risk is linked to the assumption of life-long exposure at the limit. Thus any increased risk per year's exposure for younger women is counterbalanced by the decreased risk per year's exposure for older women. Refined calculations could be made by considering only the risk to females and by taking account of what is known about the distribution of latent periods for radiation-induced breast cancer after a brief exposure. Young adult women are highly represented amongst those occupationally exposed in the medical services. This is just another reason for making sure that X-ray departments are well-run. Specific restrictions on exposure of female staff beyond those already recommended by ICRP may seem unjustified.

Biology of breast cancer

Since radiotherapy is commonly part of treatment for breast cancer and since the untreated breast is bound to receive some dose (depending on the technique used), the observations discussed above would lead to the prediction that subsequent frequency of breast cancer would be raised in the untreated breast and that this increase in frequency would be more conspicuous the younger the age at which the treatment had been given. Both predictions appear to be supported by observations. At ten to 15 years after treatment of breast cancer the frequency of cancer in the untreated breast was found to be four-fold greater than that expected from national statistics (Brinkley and Haybittle, 1968). The risk of occurrence of a second primary breast cancer in the other breast was markedly dependent on the age at diagnosis of a first breast cancer, in one survey being 84-fold higher for those aged 20–24 years and four-fold higher for those aged 40–44 years at the time of the first diagnosis (Waterhouse and Prior, 1975). However there is as yet no evidence to tell how much of these observed differences may be attributed to biological factors and how much, if any, to radiotherapy. Known biological factors, such as cystic mastitis and the length of the time interval between the menarche and the first pregnancy, seem responsible for only a three to four-fold difference in risk of breast cancer (MacMahon and Brown, 1973). Now that the high radiation sensitivity of the human breast is established, the effect of radiation dose on the untreated breast must be evaluated before accepting quantitative conclusions about genetic or other influences derived from epidemiological reports on the occurrence of a second cancer in individuals who have already had a first breast cancer.

Concluding comment

No attempt is made here to make recommendations about the use of radiotherapy in breast disease or about mammography as a screening procedure aimed at detecting early breast cancer and so improving the results of treatment. In each case the balance of risk and benefit can be established only by careful study of *all* the factors involved. The purpose of this brief review is merely to provide a short summary of quite recently acquired information about just one of these factors.

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Book review

Growth Kinetics of Tumours (*Cell population kinetics in relation to the growth and treatment of cancer*). By G. G. Steel. pp. xi+351, illus., 1977 (Oxford, Clarendon Press) £15·00.

This book provides us at last with a comprehensive, authoritative and very readable account of cell kinetics in tumours. It fills a gap that has been glaringly obvious. This volume must be considered an essential part of any Library on Cancer Research, and at £15·00 for 350 fact-filled pages it also represents excellent value.

The information is clearly presented with plenty of diagrams, and Dr. Steel stresses the *evaluation* of data rather than simply its accumulation. There are two chapters on the overall growth rate of tumours and the theory of growing populations of cells. These are followed by an account of the techniques available to study tumour cell production and cell loss. The most commonly used technique (percent of labelled mitoses) is the subject of a whole chapter, including a very useful summary and intercomparison of the computer programmes available for analysing such data. Other less commonly used techniques are comprehensively surveyed, although surprisingly little space is allotted to cytofluorometry and cell sorters.

Dr. Steel provides an excellent summary of the proliferation studies that have been reported for both experimental and human tumours. He stresses the importance and the inadequacy of data on solid tumours, and perhaps his account will stimulate further work. He analyses the relevance of tumour size, of transplantation history and of the microanatomical structure in experimental tumours and highlights the lack of data on spontaneous tumours.

The chapter on stem cells presents an unbiased account of the evidence for and against their existence, and is a useful introduction to the clonogenic cell assays available for use on treated and untreated tumours. This leads into the discussion of the response of tumours to various cytotoxic agents. He emphasizes that to the cell kineticist cytotoxic drugs and radiation would naturally be classed together. This book may help to encourage interaction between groups whose interest at present is restricted to either drugs or radiation.

The book ends with a glossary of terms (essential for any newcomer) and a list of "growing points" which are likely to encourage other researchers to include cell kinetic analyses in their future work. Armed with this book they could do so with confidence.

A most stimulating and rewarding book to read.

J. DENEKAMP.

1978 *British Journal of Radiology*, *51*, 406–413

The misplaced caecum and the root of the mesentery

By G. M. Steiner, D.C.H., M.R.C.P., F.R.C.R.

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(*Received December, 1977*)

ABSTRACT

Five cases presenting in late infancy and childhood with symptoms and signs referable to malrotation of the midgut are described.

The condition may present with jaundice, malabsorption or the signs and symptoms of intestinal obstruction due to internal hernia or volvulus. It may also result in volvulus and gangrene of the midgut. A short root of the mesentery predisposing to this event will be seen on a barium meal and follow through examination and will warn of its impending occurrence.

Problems in the neonatal period due to malrotation of the midgut are well known. Less well appreciated is the fact that malrotation can cause serious problems in older infants and children (Estrada, 1958; Pochaczevsky *et al.*, 1972; Firor and Harris, 1974).

EMBRYOLOGY

Diagnosis of the problem depends on a knowledge of the embryology of the midgut. The scheme which seems to fit the clinical facts best is that of Snyder and Chaffin (1954). They postulate that the fetal midgut loop rotates 270° anticlockwise around the superior mesenteric artery (SMA) as it returns to the abdomen from the umbilical cord. Each end undergoes rotation independently of the other (Fig. 1 and Fig. 2).

The duodeno-jejunal segment rotates behind the SMA so that the duodeno-jejunal flexure comes to lie to the left of L1 or 2. The caecocolic segment rotates in front of the SMA till the caecum lies in the RIF where it is fixed and becomes a retroperitoneal structure. Often fixation is incomplete and the caecum remains mobile on a mesentery; the cause of the "high" caecum which is generally not thought to have any clinical significance. The normal midgut therefore shows the following features:

1. The duodeno-jejunal flexure lies to the left of L1 or 2.
2. The small bowel lies mainly in the left side of the abdomen.
3. The caecum lies in the RIF but may move out of position if on a mesentery.

In a patient with malrotation any one or all of these factors may be at fault.

PATHOLOGY AND CLINICAL FINDINGS

The midgut is suspended from the posterior abdominal wall by a mesentery with a long root running from the DJ flexure to the caecum. Should the root of the mesentery be short, as in malrotation when the DJ flexure and caecum tend to approach each other, volvulus of the midgut is more liable to occur; this will first obstruct the venous blood supply leading to congestion of the bowel and then the arterial supply leading to gangrene. Chronic congestion of the bowel can give rise to malabsorption. The twist of the bowel itself will cause obstruction; if the common bile duct is twisted, jaundice will result.

Malrotation is associated with the formation of fibrous bands that usually run from the caecum across the duodenum (Ladd's bands) and thereby obstruct it. There is also an increased incidence of internal herniae with malrotation.

The patient may therefore present with:

1. Abdominal pain and vomiting due to obstruction of the bowel lumen by a twist, fibrous band or internal hernia. Obstruction of the blood supply will give rise to similar symptoms.
2. Jaundice due to twisting of the common bile duct.
3. Malabsorption due to congestion.

The abdominal pain may be intermittent and chronic, or the illness may be very acute with gangrene of the bowel leading to death.

RADIOLOGY

The radiological diagnosis of malrotation of the midgut is complicated by the fact that the caecum so frequently lies outside the RIF. It is subhepatic in 6–6.5% of cases according to Estrada, 1958. A mobile caecum has been noted in up to 36% of patients (Bruns and Lassrich, 1969). A "high" caecum cannot therefore, on its own, be regarded as pathological.

Since volvulus only occurs if the attachment of the mesentery to the post-abdominal wall, *i.e.*, the root of the mesentery, is short it would be very useful to be able to estimate its length radiologically. The feasibility of doing this was investigated in post-mortem material. The ends of the root of the mesentery were marked out at post-mortem with surgical clips with all the viscera *in situ* and then X-rayed. It soon became obvious that the left end of the root coincided with the DJ flexure but that the

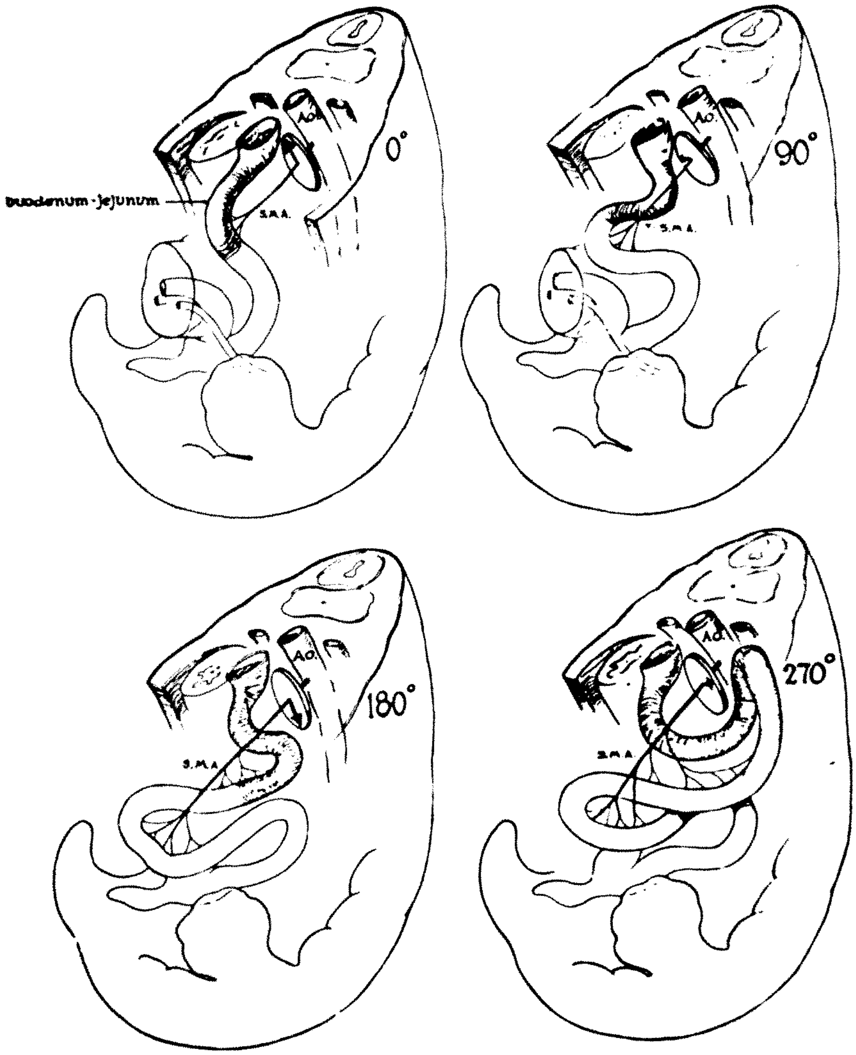


FIG. 1.

Diagrammatic representation of 270° anticlockwise rotation of duodeno-jejunal segment of midgut. Duodenum comes to lie behind the superior mesenteric artery, the DJ flexure to the left of the upper lumbar spine.

right end and the tip of the caecum did not bear a constant relationship to each other. Accordingly, the tip of the caecum was also clipped. This procedure was carried out in 23 patients (Fig. 3).

From these few patients it became apparent that the position of the tip of the caecum was very variable indeed and that the tip of the caecum could lie a considerable distance from the right end of the root of the mesentery. However, in none of the cases did the right end of the root of the mesentery lie to the right of the tip of the caecum. Thus, in none of our post-mortem cases did the length of the root of the mesentery exceed the distance from the DJ flexure to the tip of the caecum. This distance could therefore be taken to represent the maximal possible length of the root of the mesentery. In none of the cases did the DJ flexure lie in the right side of the abdomen or the tip of the caecum in the left side.

The radiological examination to outline these landmarks is a barium meal and follow through. A barium enema will not give any information about the position of the DJ flexure and therefore on the estimated length of the root of the mesentery.

CASE HISTORIES

Case 1. This little boy had been a poor feeder and constipated from birth. A barium meal had shown the small bowel and DJ flexure on the right. (Fig. 4). He failed to thrive and was readmitted at 14/12 with retching and constipation. A barium enema showed a high caecum (Fig. 5).

By putting the two barium examinations together it is easy to see he has a short root of the mesentery. This was found at operation together with malrotation leading to venous and lymphatic congestion of the small bowel. The malrotation was corrected by placing the large bowel on the left of the abdomen and freeing adhesions. The patient has done well since.

Case 2. This four months old girl suffered from persistent obstructive jaundice for which no cause could be found. A barium meal and follow through was difficult to interpret. However, in the lateral view the stomach was rotated forwards (Fig. 6). In normal babies the stomach lies horizontally across the upper abdomen and the antrum and duodenum point backward. At 18 hours (Fig. 7), there was a persistent collection of barium on the right, the small bowel lay on the right and at 24 hours the appendix lay high in the right flank.

At operation the common bile duct was twisted and blocked and the stomach had herniated through the foramen of Winslow (Fig. 8). This is an example of an internal hernia and twisted bile duct associated with malrotation.

Case 3. 50-month-old girl. Four months history of vomiting and loose motions, and abdominal distension. Plain film of the abdomen showed enormous distension of the bowel.

A barium enema showed a normal large bowel with the caecum in the RIF. Barium meal and follow through (Fig. 9), showed the DJ flexure in the wrong place (in the right side of the abdomen) and marked small bowel distension. At operation a fibrous band obstructing the distal ileum was found and resected. Usually fibrous bands associated with malrotation obstruct the duodenum so this case is unusual in this respect.

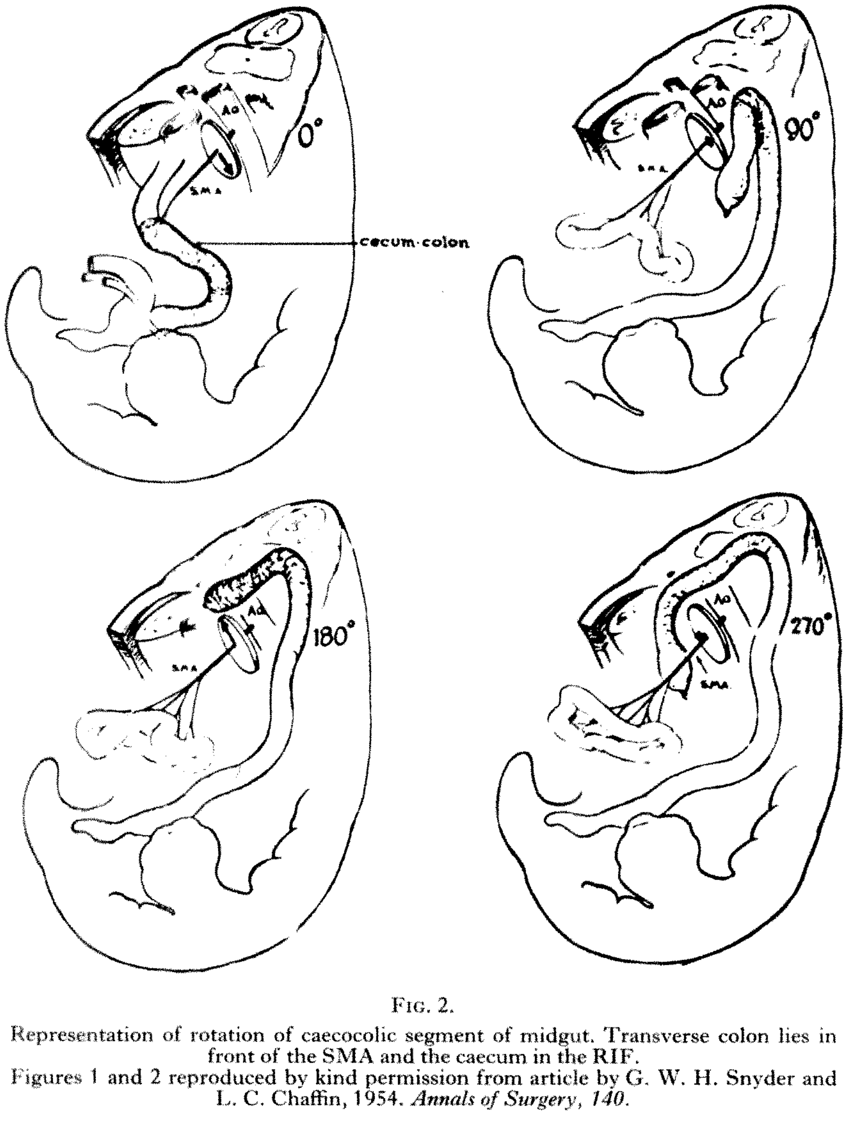


Fig. 2.

Representation of rotation of caecocolic segment of midgut. Transverse colon lies in front of the SMA and the caecum in the RIF.

Figures 1 and 2 reproduced by kind permission from article by G. W. H. Snyder and L. C. Chaffin, 1954. *Annals of Surgery, 140.*

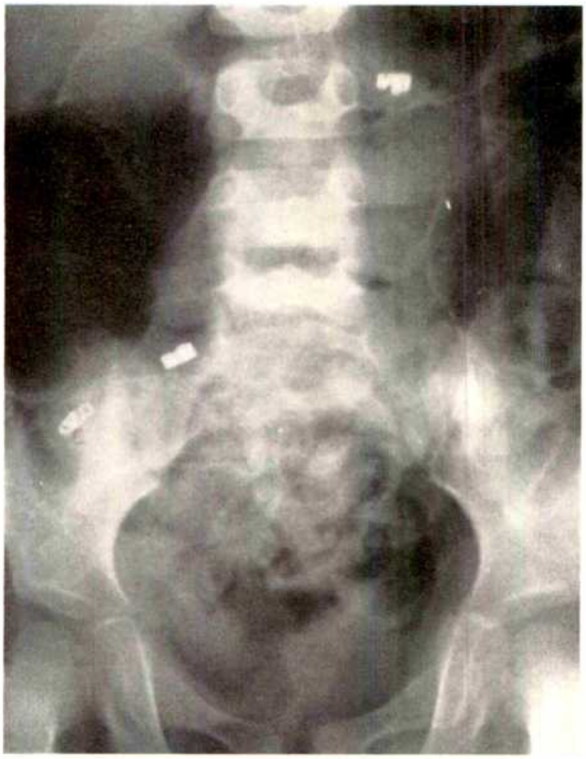


FIG. 3.

Post-mortem identification of root of mesentery. Single clips mark ends of root of mesentery, double clips the tip of the caecum.

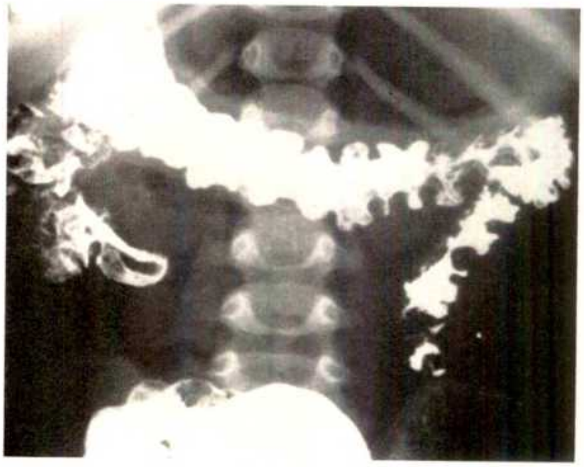


FIG. 5. *Case 1.*

Barium enema. Caecum displaced out of the RIF. The distance from the DJ flexure to the tip of the caecum (the longest likely length of the root of the mesentery) is very short.

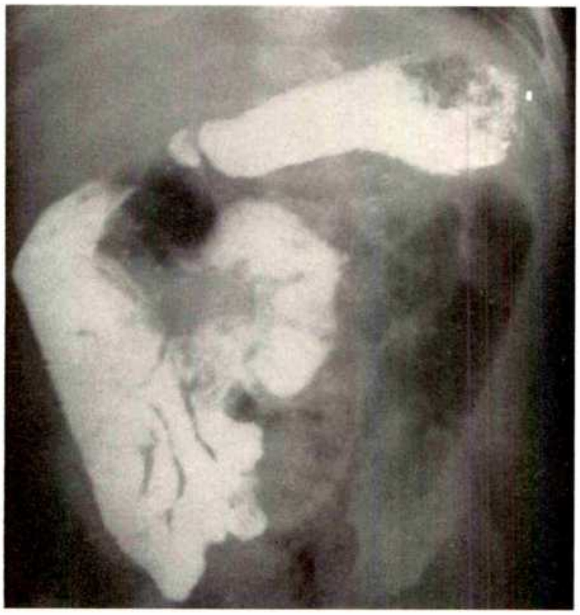


FIG. 4. *Case 1.*

Barium meal shows DJ flexure and small bowel in right side of abdomen.

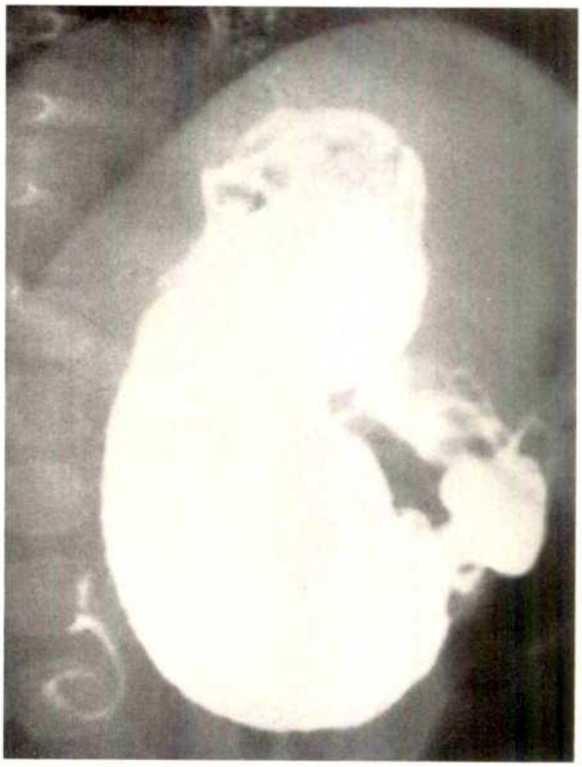


FIG. 6. *Case 2.*

Barium meal. The stomach is rotated forwards in this lateral view.

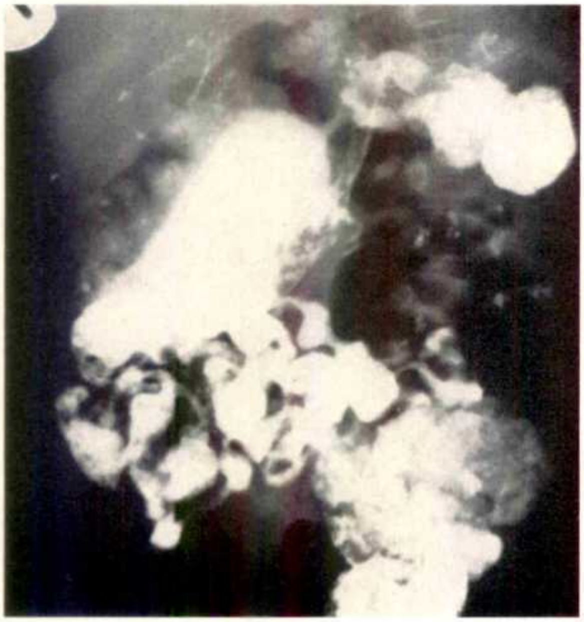


FIG. 7. *Case 2.*

Barium meal and follow through. 18 hours. Large collection of barium in the right hypochondrium. Small bowel lies on the right indicating malrotation of midgut.

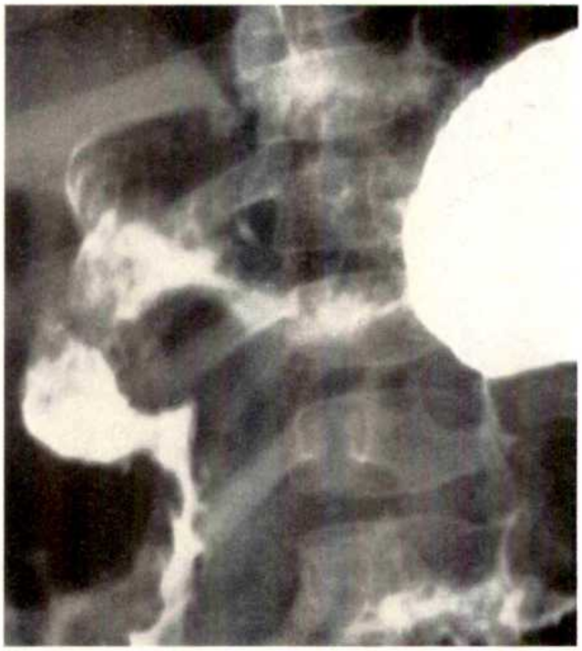


FIG. 9. *Case 3.*

Barium meal. DJ flexure and small bowel on right. The caecum in this patient was in normal position.

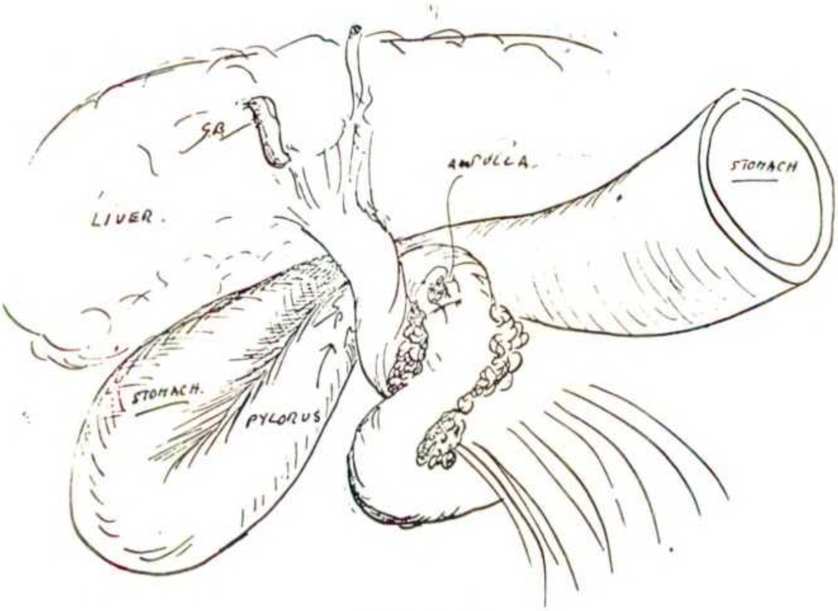


FIG. 8. *Case 2.*

Post-mortem drawing. Stomach has herniated through Foramen of Winslow. Common bile duct is twisted.

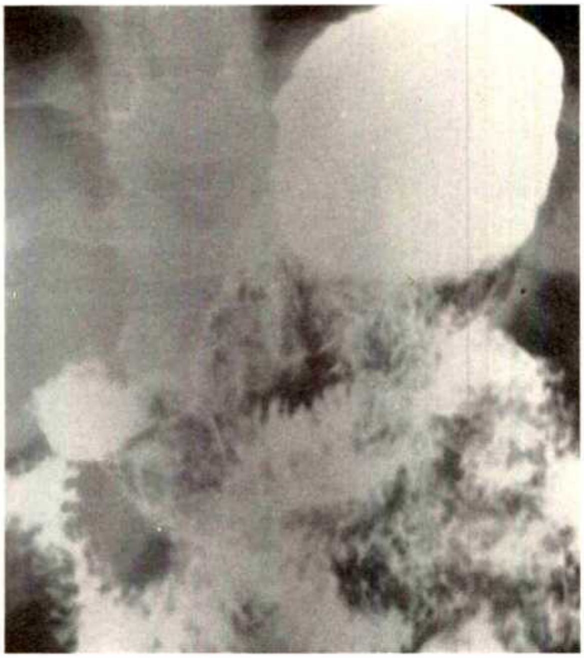


FIG. 10. *Case 4.*

Barium meal. Normal position of DJ flexure and small bowel. Plain film appeared to show the caecum in the RIF. At operation the caecum lay in the left hypochondrium and malrotation was present.

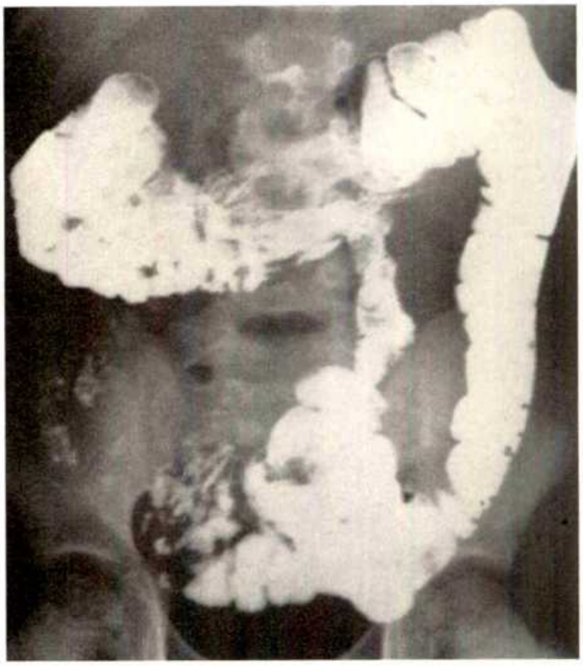


FIG. 12. *Case 5.*

Barium enema. Caecum in right hypochondrium. Distance from DJ flexure to tip of caecum very short.

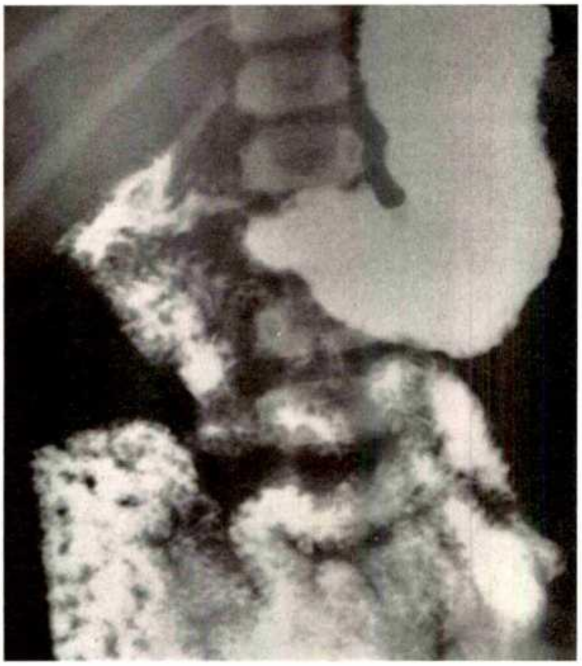


FIG. 11. *Case 5.*

Barium meal. DJ flexure slightly low. Small bowel displaced to right.

Case 4 12 years. This boy was first seen at seven years when he complained of right sided abdominal pain and vomiting. He was investigated in 1971, 1972, 1973, 1976 and labelled "periodic syndrome". An upper intestinal study (Fig. 10) was normal. A plain film of the abdomen appeared to show the caecum in the right flank. An IVP and cystoscopy were normal. Finally, he was admitted as an emergency and at operation for suspected appendicitis his caecum was found in the left hypochondrium. The mesentery was congested and there were numerous adhesions. These were lysed and the malrotation corrected. He has done well since.

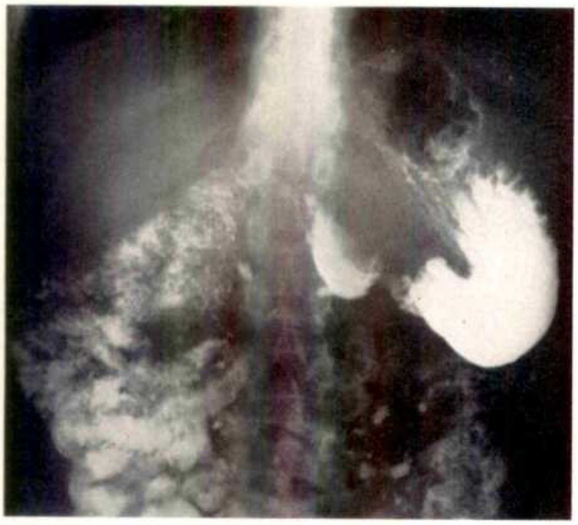
This is an example of chronic intermittent volvulus giving rise to intermittent symptoms. It underlines the need to carry out a full barium meal and follow through examination. The position of the caecum cannot be reliably judged on plain films in children since the filled sigmoid colon often comes to lie in the RIF and can be mistaken for the caecum.

Case 5 six years. Seen in casualty with acute abdominal pain. Thought to have had pneumonia but a barium meal and follow through arranged (Fig. 11). The DJ flexure was displaced caudad and overlay the lumbar spine. The small bowel was displaced to the right although it still overlay the spine. The caecum was "high" in the right hypochondrium (Fig. 12). Subsequently the patient was admitted with another acute attack of abdominal pain and at operation was found to have a volvulus with gangrene of the whole small bowel. At post-mortem, the root of the mesentery was only 5 cm long.

This case was mistaken for a simple "high" caecum. However, from the positions of the DJ flexure and of the caecum, the length of the root of the mesentery was also short radiologically and the diagnosis of malrotation should have been taken more seriously.

Discussion

The significance of the radiological signs of malrotation appears to vary with age. There is general agreement that malrotation is a definite cause of problems in the neonate.



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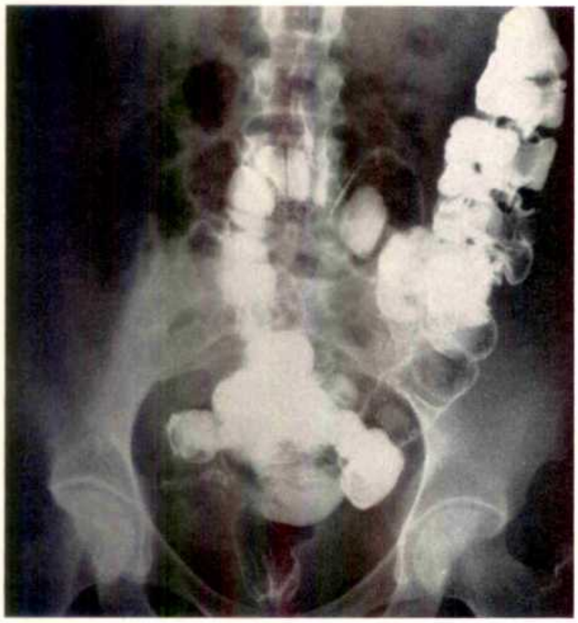

B

Fig. 13.

Adult patient complaining of abdominal pain. The root of the mesentery is long. Malrotation present

(A) Small bowel on right.

(B) Caecum in left side of pelvis.

Every radiologist must come across adult patients with a displaced DJ flexure, displaced small bowel and caecum (Fig. 13 A and B).

These patients usually have a barium examination for abdominal pain and although Friedland *et al.* (1970) have described similar cases which have been relieved by the removal of Ladd's bands crossing the duodenum, these patients are often regarded as suffering from psychosomatic disease and are not treated surgically. However, one may wonder whether the "psychosomatic" symptoms are not really due to malrotation. These patients do not suffer from the catastrophic complication of acute volvulus and gangrene of the midgut. Either the root of the mesentery is still quite long in spite of the malrotation or enough adhesions have formed in the course of years to prevent an acute volvulus.

The group of patients described in this paper, neither neonates nor adults but in the first decade and a half of life, are more difficult to assess. It is in these patients that a radiological assessment of the root of the mesentery would be most useful. An accurate assessment is, unfortunately, impossible The left end is accurately marked by the DJ flexure but the right end does not coincide with the tip of the caecum. All one can say is that the tip of the caecum marks the greatest length possible and that the right end of the root of the mesentery lies medial to it. The distance from the DJ flexure to the tip of the caecum can, therefore, be taken as a rough guide to the maximum possible length of the root of the mesentery.

How short is too short? No criteria exist for this. However, a mental comparison between the expected length and the estimated length will allow a subjective opinion to be given.

Fibrous bands (Case 3) or internal hernia as the cause of the symptoms (Case 1) should also be considered in association with malrotation.

Conclusion

Abdominal pain is very common in childhood, symptomatic malrotation very rare. However, if the pain is persistent and debilitating, malrotation should be considered. It should also be considered as one of the rarer causes of jaundice, malabsorption, intestinal obstruction and failure to thrive. The examination of choice is a barium meal and follow through. When the condition is found and the root of the mesentery is estimated to be short, volvulus and gangrene of the small bowel are definite possibilities and an urgent surgical opinion should be sought. Fibrous bands as the cause of symptoms should also be considered.

ACKNOWLEDGMENT

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Book review

The fundamentals of X-ray and radium physics. By Joseph Selman, pp. xxx+586 illus., 6th edn, 1977 (Charles C. Thomas, Springfield, Illinois, USA), $18.75.

This is the sixth edition of the book, first published in 1954. One might, from the title, expect to find a treatise in depth of fairly advanced physics underlying the use of X rays and radioactivity. It is however designed as a teaching text for X-ray technicians, *i.e.* radiographers. I would like to quibble over the title a little further in that only about half of the book is really devoted to physics; the other half deals with radiography and technology with a little physics included where necessary to clarify the explanations.

Having said this, it must be stated that the book is excellent, comprehensive, and achieves what the author states is his purpose. The material is based on lecture notes and other data used in the instruction of student technicians over a period of years. There is a shortage of textbooks on physics at a level suitable for radiographers and X-ray technicians but this book fills that gap very well.

Having failed to discern any obvious errors, there are nevertheless a few matters to which I would like to draw attention, since the book is intended to be instructive to those who may not be knowledgeable in the field. Surely energy is not so much the actual or potential ability to do work, but rather the amount of work that a body is able or potentially able to do. One gets the impression from reading the section on Fundamental Units, that CGS units may be used as an alternative to MKS, whereas certainly in Europe the CGS system is no longer in common use. When discussing the physical concept of energy, the conventional statement that the total amount of energy in the universe is constant is quoted and a few paragraphs later Einstein's equation is referred to and used to explain how mass can be converted to energy. Perhaps an amplifying comment about the law of conservation of energy might not be out of place for the benefit of the student who may have only a slight physics background.

Having already praised the comprehensive nature of the text of the book, nevertheless there is a section on Solid State Physics incorporated in the chapter in which X-ray tubes and rectifiers are discussed which is out of place in a book of this level, in that it is doubtful whether all but an extreme minority of radiography students will follow it. The diagram of the energy levels in a conductor does not bring out clearly that the high conductivity in a metal arises from the fact that there is a high population density of electrons in the conduction band, thus allowing the possibility of current flow in the metal with small applied potential.

It is necessary for the reader to be aware, when learning about the electric main supply system, that the three-wire system in the USA is not the same in terms of voltage or conductor arrangement as the three-phase system which is discussed later in the same chapter.

When describing the way in which radium should be handled, reference is made to a 2 inch protective lead block in association with a lead glass visor, with a lead equivalent of 6 mm. It is customary in a busy department to have at least 4 inch of lead between the operator's body and the radium, and in some hospitals a moveable lead glass block with at least a 4 inch thickness of lead glass is used between the operator's face and the radium, a facility useful for identifying numbers on radium needles. The treatment of the subject in this section perhaps derives from the fact that the book first appeared in 1954; in view of the current trend towards replacing radium by artificial radionuclides, this section needs to be updated.

A half only of the book is devoted to physics; the other half is devoted to an excellent discussion on technological matters in which the scientific basis is always explained, and the practical details relating to radiographic procedures are described fully with a great deal of technical information included. All in all, a very good book for a student radiographer to obtain.

N. W. RAMSEY

1978, *British Journal of Radiology*, *51*, 414–419

Transcatheter embolisation of bone tumour arteriovenous malformations

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Abstract

Arteriovenous malformations complicating benign bone tumours may not be amenable to surgical treatment either because of their extensive size and likelihood of recurrence or because of their location. Transcatheter embolisation may then be used either as the definitive treatment or as a prelude to safe surgical intervention. Patients presenting with arteriovenous malformations in association with polyostotic fibrous dysplasia and vertebral haemangioma are presented who were treated by transcatheter embolisation, using Oxycel and Gelfoam. A haemodynamically significant shunt was obliterated in one patient and in the other an excellent clinical response was obtained facilitating subsequent surgical management.

Transcatheter arterial embolisation has now become an established radiological technique with an increasing range of clinical applications. These include treatment of vascular abnormalities and tumours of the central nervous system (Djindjian *et al.*, 1973), bleeding from the gastrointestinal tract (Reuter *et al.*, 1975), management of renal, hepatic and other neoplasms (Goldstein *et al.*, 1976) and of arteriovenous malformations at peripheral sites (Olcott *et al.*, 1976). We wish to present a further application of this technique, i.e. in bone tumours with associated arteriovenous malformations.

Arteriovenous malformations complicating benign bone tumours represent an unusual entity. They may be of clinical significance, as in the cases presented, because of a hyperdynamic circulation producing left ventricular failure or alternatively, because of their anatomical location and mass. Where surgery is contraindicated or hazardous, transcatheter embolisation may be employed either as the sole definitive treatment or as a prelude to safe surgical management. One of these patients presented with polyostotic fibrous dysplasia and multiple arteriovenous malformations which were considered surgically inoperable. The other patient

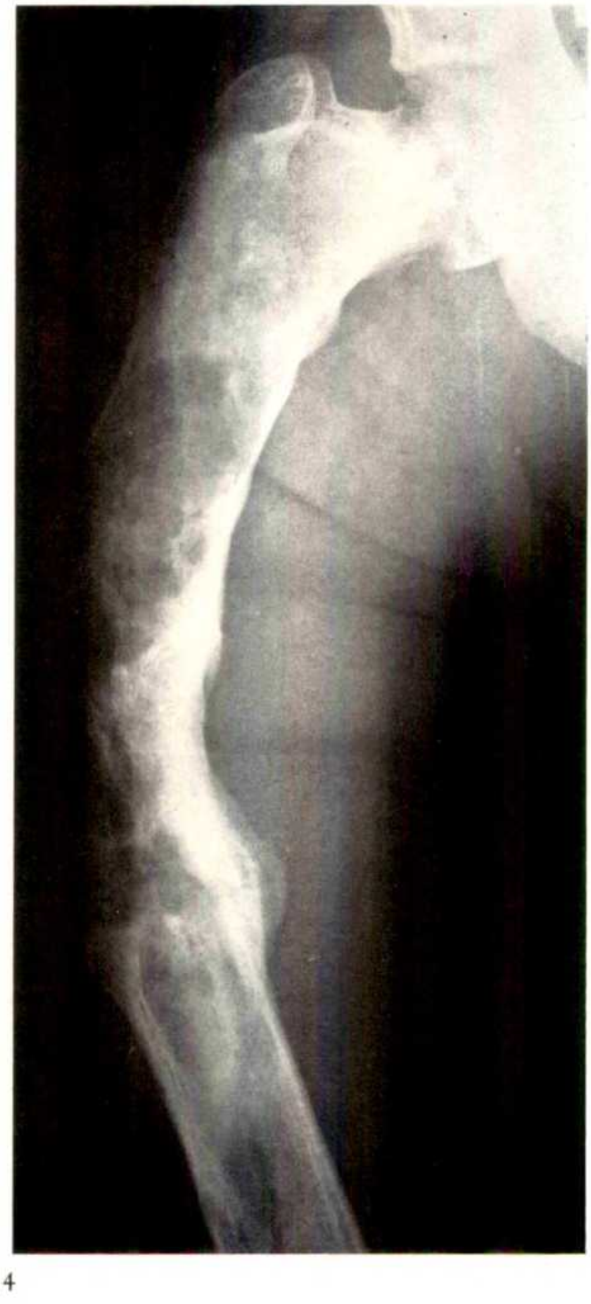

Fig. 1.

Fibrous dysplasia; the femur is bowed and contains translucencies and areas of ground-glass density. An incomplete transverse fracture is present.

presented with polycythaemia and a vertebral haemangioma producing paraplegia; embolisation in this patient was used initially to decompress the cord and later as a preoperative technique, facilitating surgery.

MATERIALS AND METHODS

Embolisation in both patients was carried out under local anaesthesia using a French-7 endhole catheter. Oxycel (oxydised cellulose) was soaked in the patient's blood, then cut into fine particles, and injected in saline in a 5 c.c. syringe under low pressure. After each shower of emboli were introduced, meglumine iothalamate 60% w/v (Conray 280) was injected to assess the degree of obstruction. In patient No. 2, gelfoam, i.e. sterile, absorbable gelatin sponge (Upjohn Co., Kalamazoo, Michigan) cut into particles of 1–2 mm, and soaked in saline, was also used. Embolisations were carried out on three consecutive days in patient No. 1, and separate embolisations were performed, three months apart, in patient No. 2.

Patient No. 1

A 24-year-old male was referred complaining of pain, swelling, increased heat and enlarged superficial veins of his right lower limb. A diagnosis of fibrous dysplasia was made when he was three years old and he had been hospitalized on many occasions for fractures of his right femur.

On examination, he had an asymmetrical skull and pigmented spots on his lips. He had a collapsing pulse of 120/minute, BP 140/60. His right lower limb was deformed, the femur bowed anteriorly, and there was true shortening of 6 cm. Skin pigmentation and varicose veins were present on the medial aspect of the lower leg. Skin temperature and arterial pulses were increased compared with the

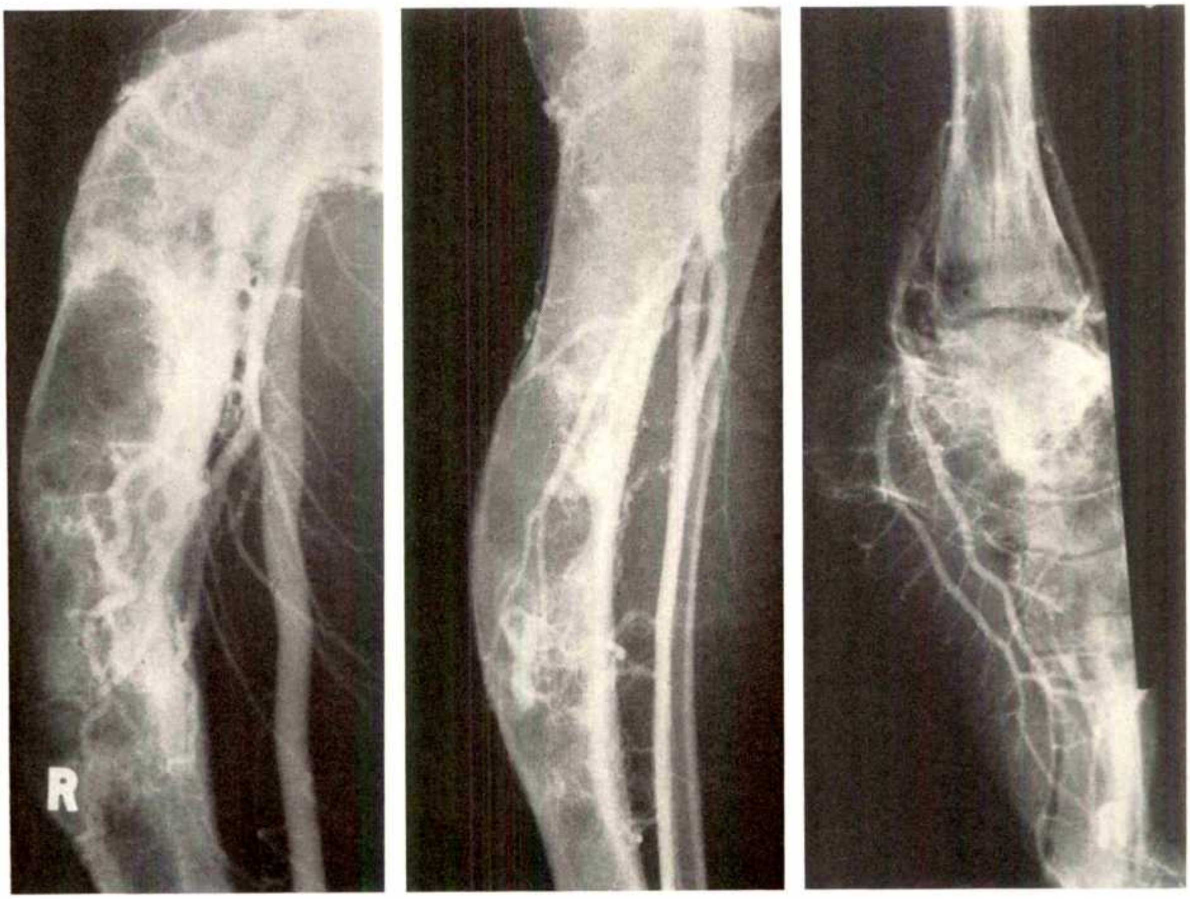

FIG. 2.

Right femoral angiogram. All vessels are hypertrophied. Numerous malformations involving the entire femur, tibia and talus.

left lower limb. A harsh bruit was heard over the common femoral artery and a machinery murmur was present over the calcaneum. The Nicoladoni-Branham sign was present on compression of the right common femoral artery, i.e. on continuous compression of this artery, the pulse changed from 120 to 90, indicating a locally significant haemodynamic shunt.

All biochemical and blood tests were within normal limits. Skeletal X rays demonstrated the classical signs of polyostotic fibrous dysplasia, involving the skull, left first and second ribs, the right ischium, femur and tibia. An incomplete fracture of the mid femoral shaft was seen (Fig. 1). A right femoral angiogram demonstrated enlargement of all arteries of the leg with numerous vascular malformations involving the femur, tibia and talus (Fig. 2). There were no extra osseous malformations.

The high pulse rate and response to compression of the common femoral artery indicated a highly significant high output state through this limb.

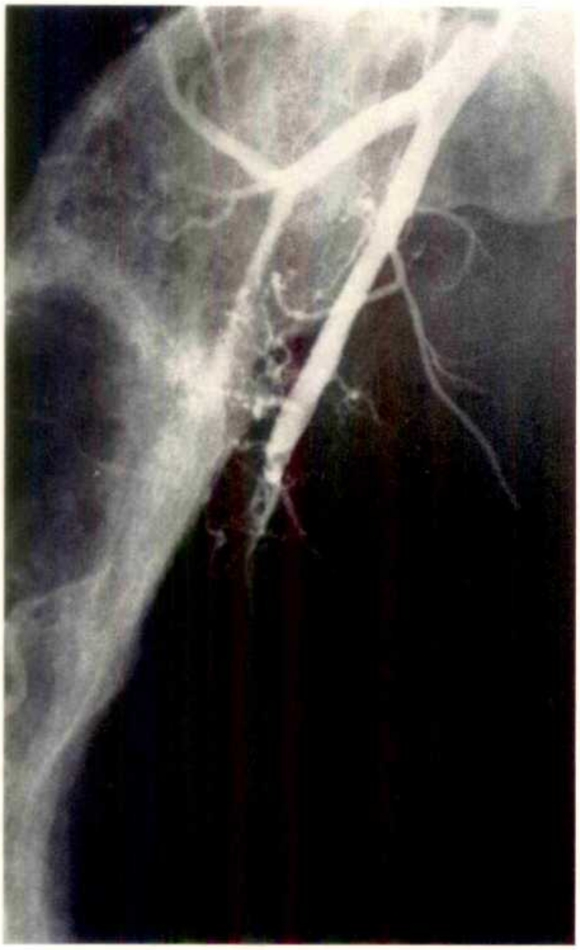

Fig. 3.

Post embolisation of profunda and circumflex arteries. Femoral arteriovenous malformations are obliterated.

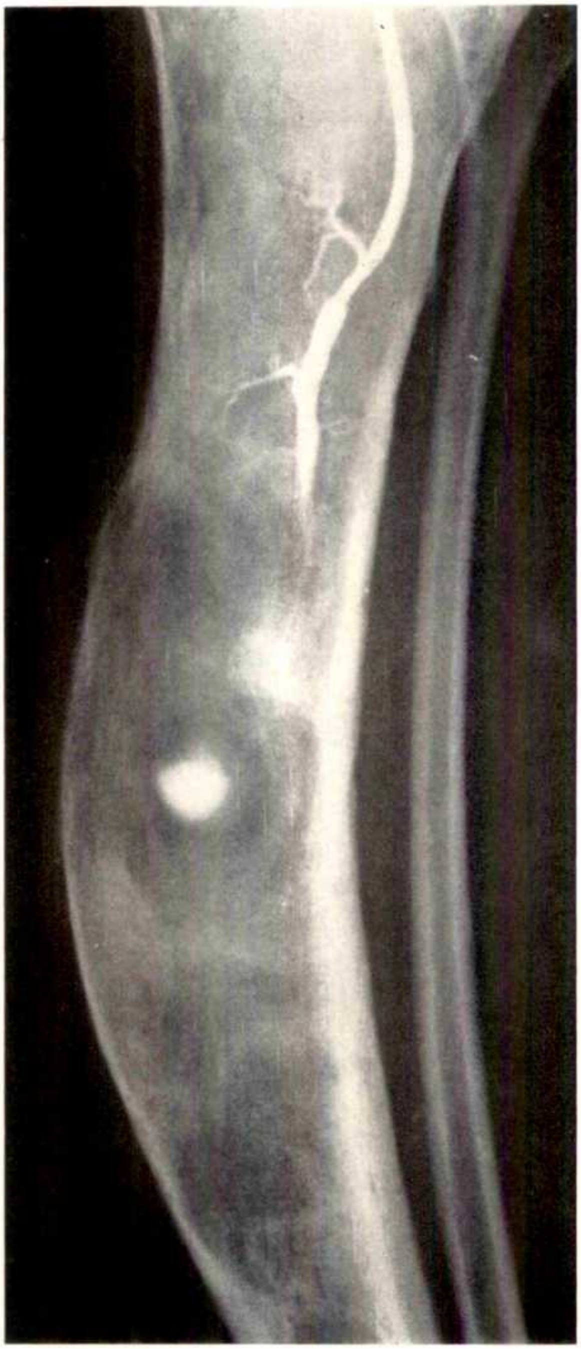

Fig. 4.

Post embolisation of osseous branches of anterior tibial artery. Central pool of contrast remains from earlier test injection. Typical bony changes of fibrous dysplasia.

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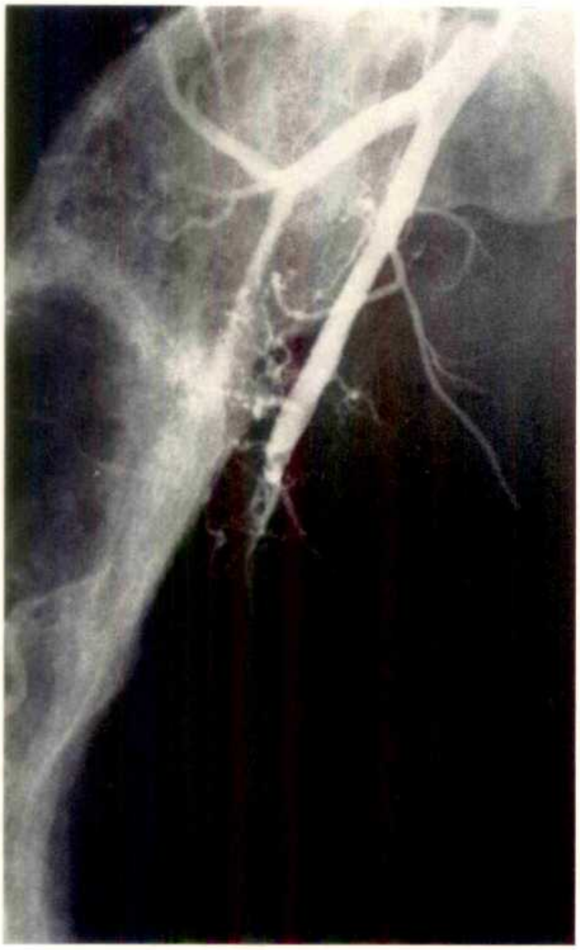

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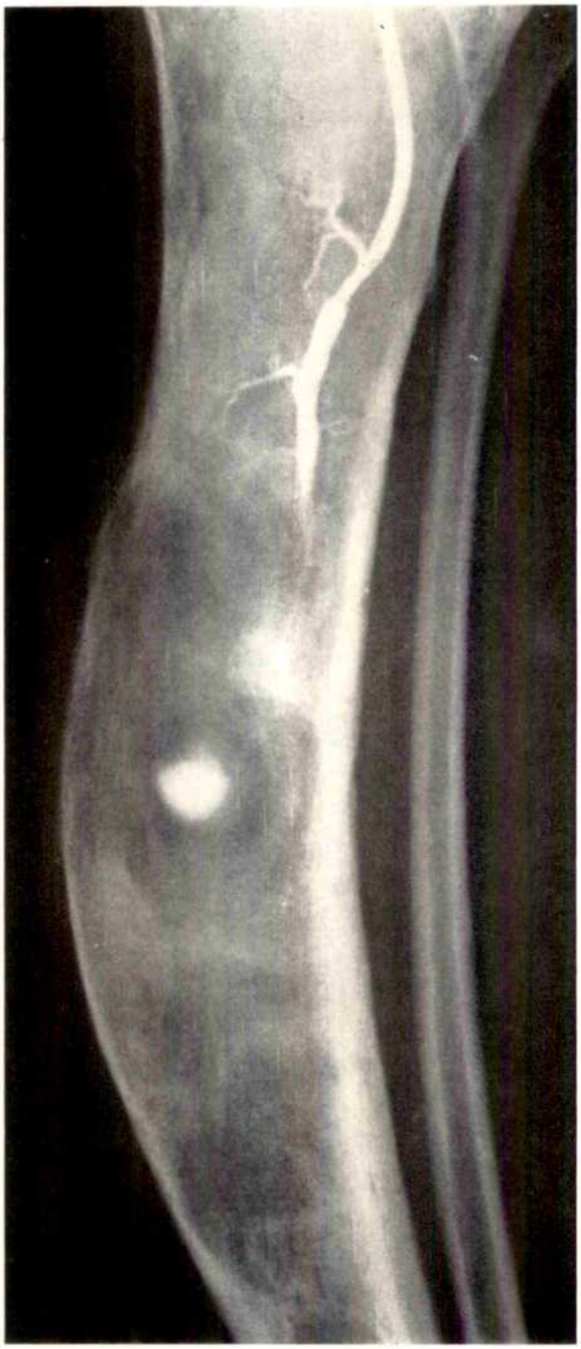

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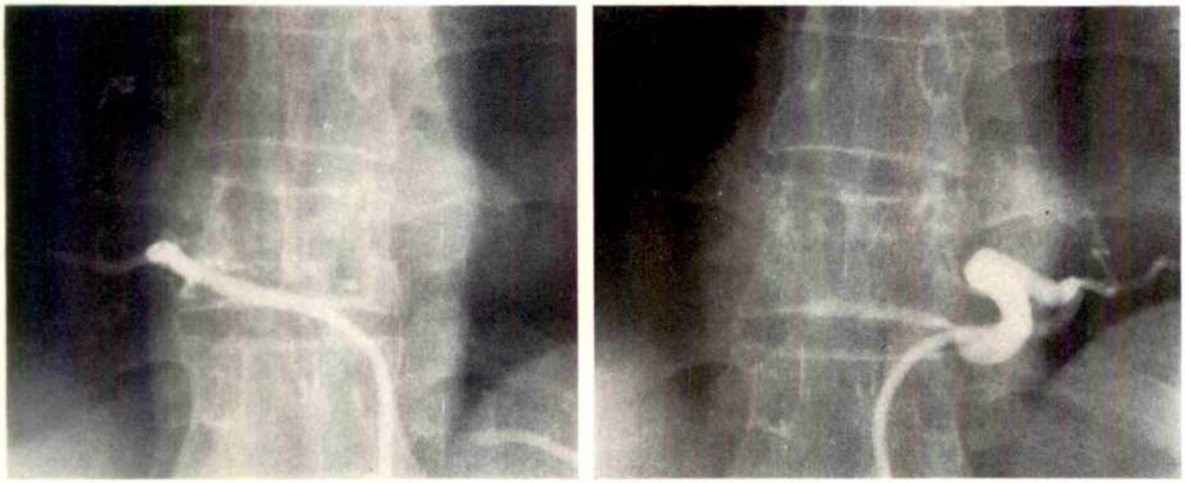

FIG. 7.

Bilateral selective 9th intercostal angiography, post embolisation. Main arteries are patent but vascular abnormality is occluded. Note hypertrophied left intercostal.

Red cell volume was increased at 62 ml per kg (normal 30 ± 8.5).

X ray of the spine revealed a lytic process involving the body of D9, with expansion of the left pedicle. A bilateral paravertebral mass was present (Fig. 5). Tomography revealed prominent trabecular strands suggesting the possibility of an haemangioma with paravertebral extension. A bone scan revealed a solitary area of slightly increased uptake at T9. Possible causes of secondary polycythaemia were investigated but none was found. It was assumed that the dorsal vertebral anomaly was secreting erythropoietin. Selective intercostal angiography, from T7 to T11 inclusive, revealed a vascular mass supplied by both the right and left 9th intercostal arteries involving the body and supplying the paravertebral mass and extending posteriorly into the pedicle (Fig. 6). A minor contribution to the anomaly was also supplied by the left 8th and left 10th intercostal arteries. The artery of Adamkiewicz was not supplied by these vessels or those of adjacent vertebrae.

A decompressive laminectomy was considered hazardous in this patient so embolisation was performed with a view to reducing the vascularity prior to surgery and possibly by itself resolving the cord compression. Selective embolisation of the right and left 9th intercostal arteries was performed using a combination of Oxycel and Gelfoam (Fig. 7). During the embolisation procedure, there was considerable improvement in power in the left leg which continued to improve dramatically over the next 12 hours. Improvement continued over the next two weeks with almost total return of power to the lower limbs and a return of vibration sense. Because of this response surgery was deferred. Ten weeks following embolisation weakness again recurred in the legs. A repeat angiographic study revealed some recanalisation of the vessels in the arteriovenous malformation. Embolisation was again performed, using Oxycel, with improvement in symptoms. As it was apparent that the material being used was being slowly reabsorbed surgery was instituted with ligation of the intercostal arteries bilaterally from T7 to T10 inclusive via a transthoracic approach. The patient's condition has continued to improve slowly since this time, and a decompressive laminectomy has not been considered necessary. A biopsy of the paravertebral mass was obtained and this revealed the classical features of an haemangioma. There were no histological features of malignancy.

DISCUSSION

Transcatheter arterial embolisation is now an accepted means of treating or complementing surgical management of arteriovenous malformations (Olcott *et al.*, 1976). The technique may in itself be curative or may be repeated, if necessary, as the main arterial channels are not embarrassed. Surgical intervention, by interrupting the main arterial channels, makes subsequent surgical management difficult and embolisation impossible if there is a recurrence of the malformation. It is more satisfactory if the feeding arteries to a malformation are occluded at the very site of the malformation—the aim of embolisation being to induce natural thrombosis by means of a foreign substance. We have applied this same rationale to bone tumour arteriovenous malformations. Both of these patients presented with unusual arteriovenous malformations of relatively common pathological entities.

Polyostotic fibrous dysplasia is characterized histologically by the proliferation within bone of vascular fibrous tissue (Warrick, 1973). This has not previously been reported as producing a haemodynamically significant vascular malformation. That this complication was not due to repeated bone trauma is substantiated by the fact that vascular malformations were also present in the tibia and talus which did not suffer trauma. It was presumed that this lesion would produce early left ventricular failure. Surgical intervention was not considered feasible in this patient due to the multiplicity of the anomalies and the probability of their recurrence. If recurrence occurs following embolisation in this patient, it will be possible to re-embolise, preferably with a non-absorbable medium, through the still patent main channels.

Polycythaemia has not previously been reported with a vertebral haemangioma. Following the surgical intervention in this second patient, a histological diagnosis of haemangioma was confirmed and there were no features of malignancy. Polycythaemia has not recurred and the haemoglobin has remained stable since surgery at 11.8 g/100 ml. Only a few cases of haemangioma producing cord compression are reported in the literature (Hekster *et al.*, 1972) and therapeutic embolisation has been recorded in single case reports (Benati *et al.*, 1974, and Hekster *et al.*, 1972). It should be emphasised that in these patients the artery of Adamkiewicz was excluded as being a contributor to the bone anomaly by extensive selective intercostal angiography. Inadvertent embolisation of this vessel will produce paraplegia and excessive introduction of contrast, i.e. greater than 3 c.c. of meglumine iothalamate 60% w/v, may produce cord damage (Kardjiev *et al.*, 1974). The good results reported by the above authors and found also in this patient are probably due to a decompressive effect secondary to collapse of angiomatous blood spaces. Had a non-absorbable medium such as Isobutyl-2 cyanoacrylate been used initially, subsequent surgery would probably not have been necessary.

Encouraging results were obtained with both of these patients and there were no complications. Oxycel and Gelfoam are absorbable materials and may be completely reabsorbed within six months. However, the advantage of this technique is that, unlike surgery, the procedure may be repeated, if necessary, using a permanent occlusive agent such as Isobutyl-2 cyanoacrylate or silicone spheres. Transcatheter arterial embolisation is a feasible and useful technique in the management of arteriovenous malformations associated with bone tumours, as in other arteriovenous malformations, either as the sole method of treatment or in a complementary role to surgery.

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The lymphographic anatomy of chylothorax

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Abstract

A detailed lymphographic study of three cases of chylothorax (in thoracic duct laceration, in Hodgkin's disease and in Noonan's syndrome respectively) is correlated with the anatomy of thoracic lymph drainage to produce the following conclusions and predictions. (1) Chylothorax can only occur by laceration or obstruction of the thoracic duct. (2) After leakage of chyle into the mediastinum from a lacerated thoracic duct, it can then leak into the pleural cavity either because of damage to the parietal pleura by the initial trauma or because the pleura breaks down under the pressure of the mediastinal effusion. (3) Injury where the duct lies on the right side of the aorta is more likely to produce a right chylothorax; injury where it lies on the left of the oesophagus is more likely to produce a left chylothorax. (4) There are many collateral vessels connecting lymphatics to veins and connecting the thoracic duct to the lymphatics of the right hemithorax; it is only if these are defective that thoracic duct obstruction may cause chylothorax. (5) This chylothorax should be purely or predominantly on the left side as the thoracic duct does not drain the right hemithorax; for right chylothorax to occur, there must be obstruction of the right thoracic lymphatics as well as of the thoracic duct. (6) Chyle may reflux from an obstructed thoracic duct by two routes—via the left posterior intercostal lymphatics to the parietal pleural lymphatics, and via the left bronchomediastinal trunk to lymphatics of the pulmonary parenchyma and visceral pleura. If the bronchomediastinal trunk enters the great veins independently of the thoracic duct, the latter route will not be taken. From visceral or parietal pleural lymphatics, chyle then extravasates into the pleural cavity.

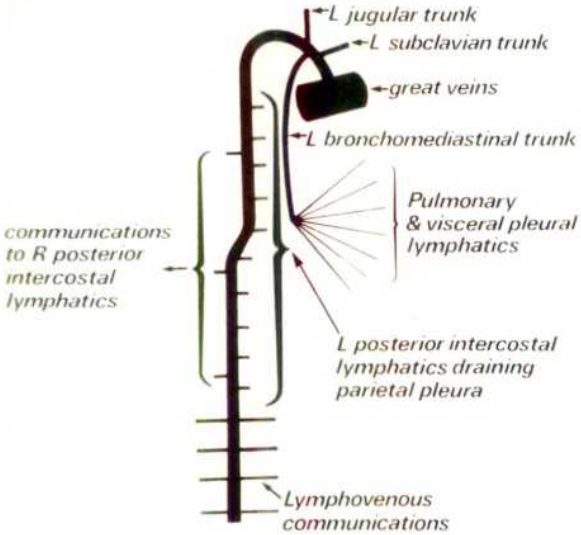
L jugular trunk
L subclavian trunk
great veins
L bronchomediastinal trunk
Pulmonary & visceral pleural lymphatics
communications to R posterior intercostal lymphatics
L posterior intercostal lymphatics draining parietal pleura
Lymphovenous communications

Fig. 1.

Chylothorax: the thoracic duct and some of its tributaries (diagrammatic). The thoracic duct ascends first on the right side of the posterior mediastinum and then on the left.

The mechanisms of chylothorax are radiologically poorly documented due to the rarity of the condition and the reputed difficulty of showing the thoracic duct and its tributaries. The cases presented here illustrate the three final pathways by which chylothorax of whatever initial aetiology is produced (Fig. 1). These are respectively: obstructed thoracic duct with seepage of chyle from distended visceral pleural lymphatics; similarly, with seepage from distended parietal pleural lymphatics; and laceration of the thoracic duct itself. Conventional lymphography via the feet was used in all cases.

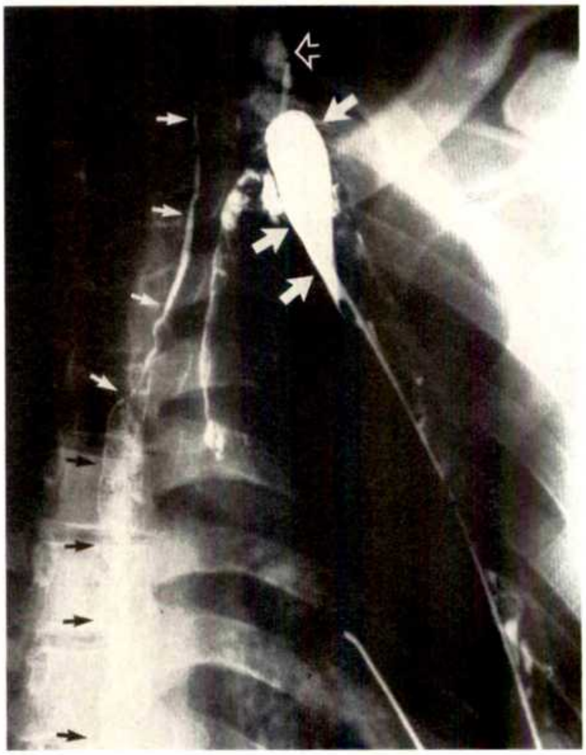

Fig. 2. *Case 1.*

Stab wound in neck causing laceration to upper end of thoracic duct. Horizontal beam radiograph with patient lying on the right side. A heavy leak of medium is seen passing into the pleural drainage tube (large arrows). The thoracic duct (small black and white arrows) is seen in its entirety. Early opacification of supraclavicular nodes (open arrow).

MATERIALS AND METHODS

Seven millilitres of ultra fluid Lipiodol were infused into a lymphatic on the dorsum of each foot with the patient on a tilting fluoroscopy table. As soon as the medium reached the cisterna chyli, the patient was tilted head up by 45 deg. so that emptying of the medium from the thoracic duct into the great veins was delayed. This kept the thoracic duct

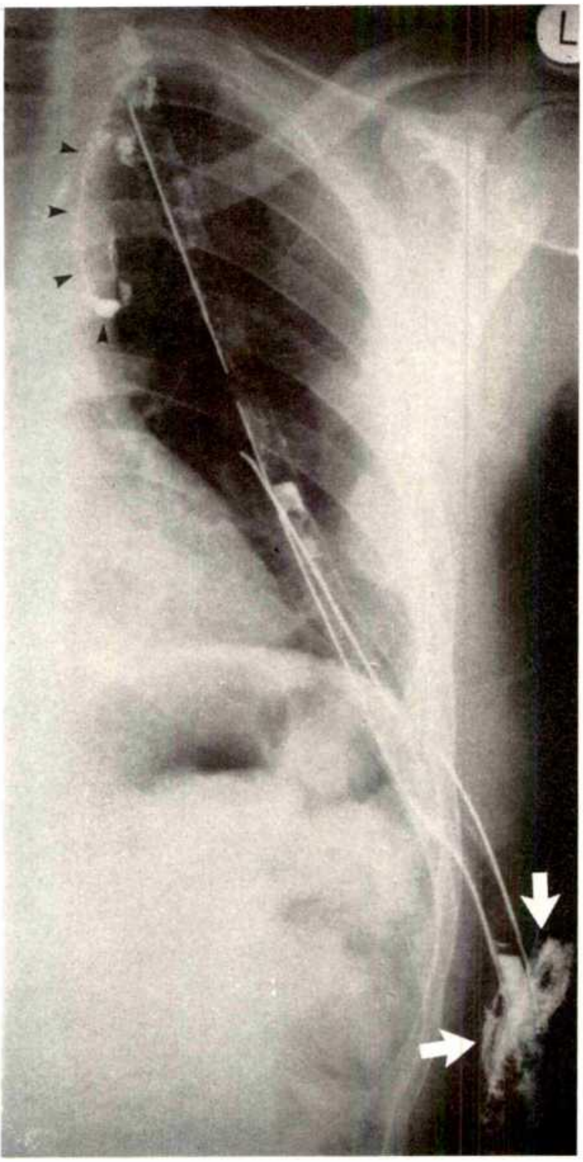

FIG. 3. *Case 1.*

Drops of contrast medium are flowing out through the pleural drainage tube, and some has leaked onto dressings on the skin (arrows). Some medium has leaked into a loculus of the pleural cavity (arrow-heads).

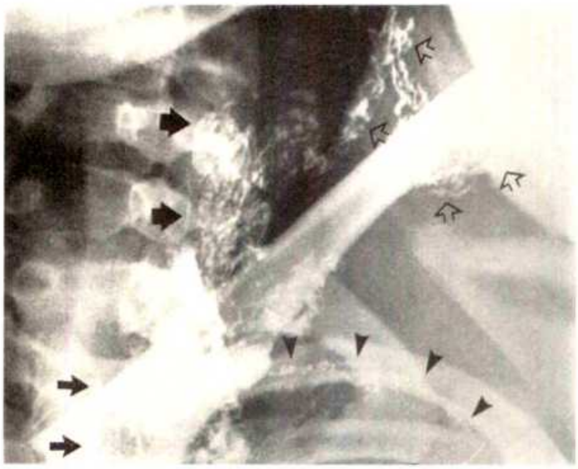

FIG. 4. *Case 2.*

Enlarged left supraclavicular nodes due to Hodgkin's disease compressing thoracic duct. There is reflux into the left 2nd intercostal lymphatic (arrow-heads) and abnormally severe reflux into lymphatics of the neck (large black arrows) and even of the arm (open arrows). Thoracic duct is seen near its upper end (small black arrows).

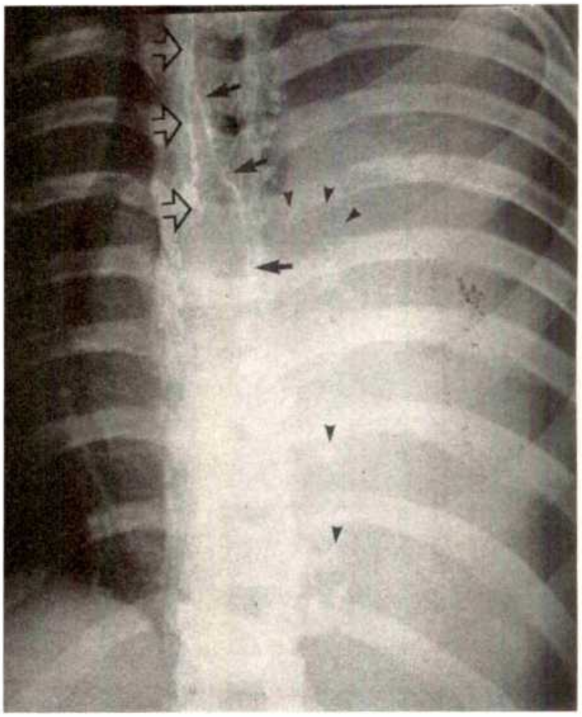

FIG. 5. *Case 2.*

Reflux into several intercostal lymphatics (arrow-heads) which seem to be tributaries of a common draining vessel (black arrows) running into the thoracic duct (open arrows). Mediastinum pushed to the right by the massive left chylothorax.

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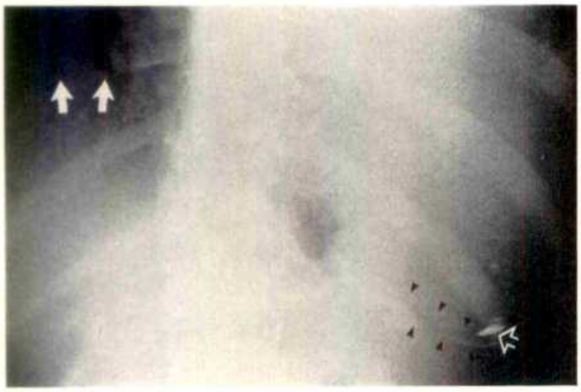

FIG. 6. *Case 2.*

Some hours later, medium is seen in parietal pleural lymphatics on the left diaphragm (arrow-heads) with extravasation into the pleural cavity (open arrow). At 24 hours, the lymphatics were no longer filled but the amount of medium lying free at the base of the pleural cavity had increased. Notice how low and concave the left diaphragm has become due to effusion. Right diaphragm (white arrows).

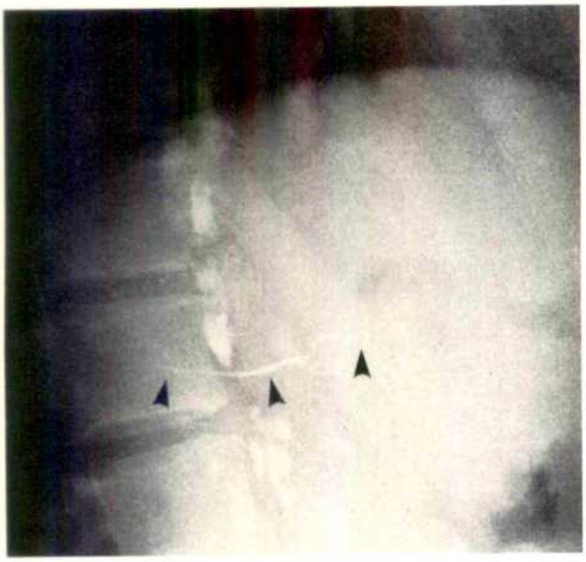

FIG. 7. *Case 2.*

Lateral view of parietal pleural lymphatics on left diaphragm.

well opacified from top to bottom, and allowed spot films to be taken in various positions.

Case 1

A black male, aged 26, had received a stab wound just above the left sternoclavicular joint. He was admitted in a shocked state with a large left haemothorax. After resuscitation and insertion of a chest drain, the stab wound was explored and a tear in the left subclavian vein repaired. The thoracic duct was found to be severed and was therefore tied off.

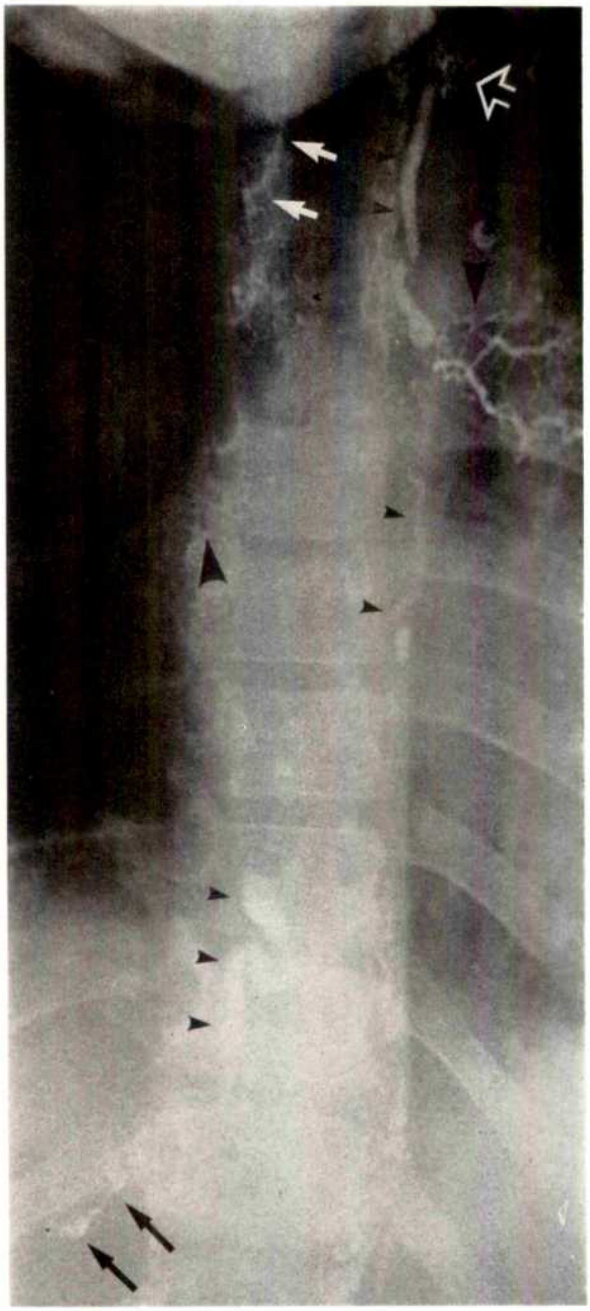

FIG. 8. *Case 3.*

Noonan's syndrome with widespread primary abnormalities of the lymphatic circulation including obstruction to thoracic duct termination. The thoracic duct (small black arrow-heads) crosses early to the left side of the mediastinum. Medium refluxes to the hilar lymphatics (large black arrow-heads). The white arrows mark a large draining vessel which may be the right bronchomediastinal trunk. Abnormal amount of reflux into lymphatics of the neck (open arrow). Also reflux into the right 12th intercostal lymphatic (black arrows).

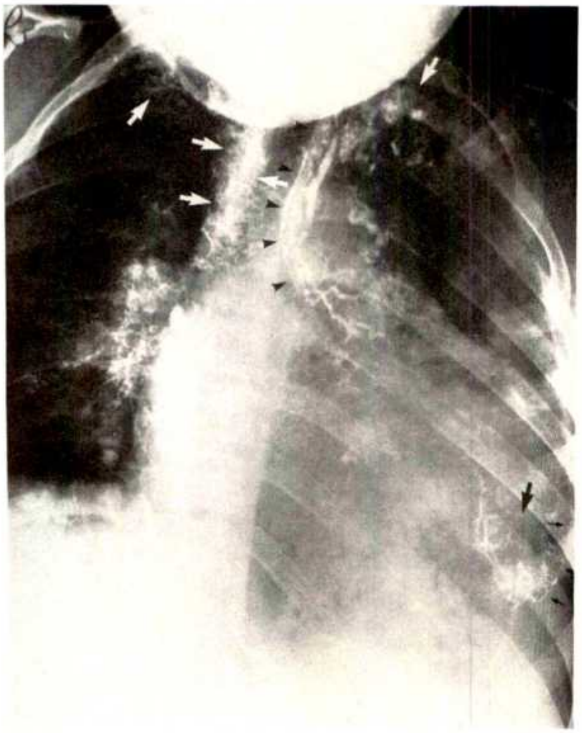

FIG. 9. *Case 3.*

Opacified lymphatics fanning out into the lungs from both hila. Especially good opacification in the lingula (large black arrows). Here a visceral pleural lymphatic (small black arrows) is pushed inwards by the pleural effusion. Opacification of a lymphatic in lateral wall of trachea and left main bronchus (black arrow-heads). Dense opacification of mediastinal and of supraclavicular lymphatics (white arrows).

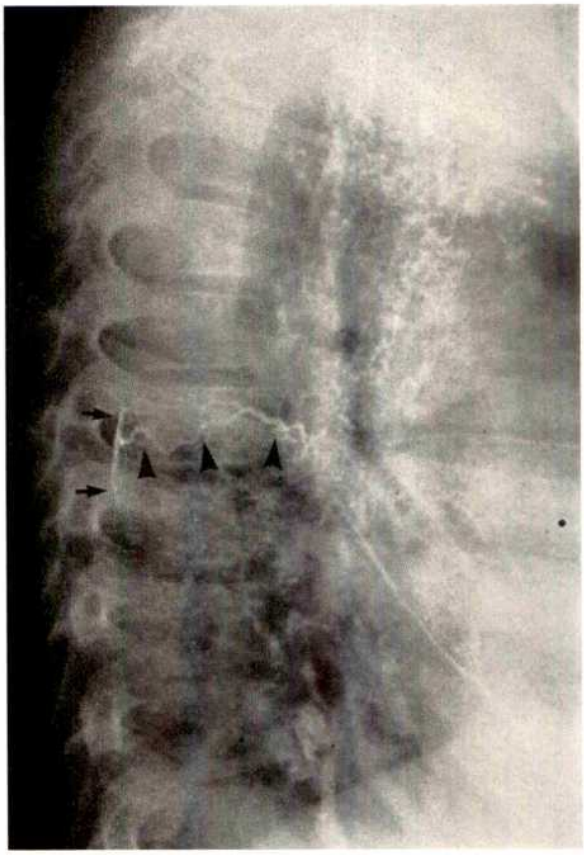

FIG. 10. *Case 3.*

Lateral view. A lymphatic (large arrow-heads) from the left hilum refluxes back into a visceral pleural lymphatic (small arrow-heads).

Post-operatively, chyle drained continuously from the left pleural space at a rate of about 600 ml daily. At re-exploration 11 days later, the pleural surfaces were roughened to encourage adhesions but it could not be determined whether the chylous leak was still coming from the severed end or from another laceration. The thoracic duct takes a bend just before entering the great veins so a stab can easily injure it in two places.

A bipedal lymphogram was performed, which showed a heavy leak from the upper end of the thoracic duct (Fig. 2). Most of the contrast medium could be seen passing directly out through the pleural drain but some did pass down into the pleural cavity, though loculated due to the adhesions (Fig. 3).

Further exploration was not required as the chylous leak decreased spontaneously and the drain was finally removed ten weeks after the injury.

Case 2

A 24-year-old white male presented with several weeks' history of loss of appetite and weight, sweating and dyspnoea. The left supraclavicular nodes were enlarged. Chest radiograph showed enlarged right sided mediastinal lymph nodes and massive left sided pleural effusion. Mediastinoscopy on the right side with biopsy revealed nodular sclerosing Hodgkin's disease. In spite of repeated aspirations of chylous fluid, the left hemithorax remained almost totally opaque due to very rapid re-accumulation.

Bipedal lymphography showed normal appearances in the lower limbs, iliac and lumbar chains, but highly abnormal appearances in the thorax. There was much reflux into the left posterior intercostal lymphatics and an abnormal amount of reflux into lymphatics of the neck and left upper arm (Figs. 4 and 5). On later films, the left supraclavicular nodes lying on the termination of the thoracic duct showed the typical enlarged and foamy appearances of lymphoma. Some hours after the infusion, the parietal pleural lymphatics lying on the left diaphragm could be seen filled with refluxed medium (Figs. 6 and 7). At 24 hours, medium which had extravasated from these vessels was lying free in the pleural cavity.

Complete investigation, including staging laparotomy, revealed this to be a stage IIB lymphoma. The patient was therefore radically treated over a period of several weeks with 3500 rad by mantle field to the upper body, a 500 rad booster dose to the mediastinum and a further 3500 rad between the diaphragm and L.3. This caused rapid regression of the chylothorax, eventually leaving only mild blunting of the costophrenic angle, and disappearance of the thoracic and cervical node enlargement.

Case 3

An eight-year-old black female showed the typical features of Noonan's syndrome (Nora *et al.*, 1974). She had

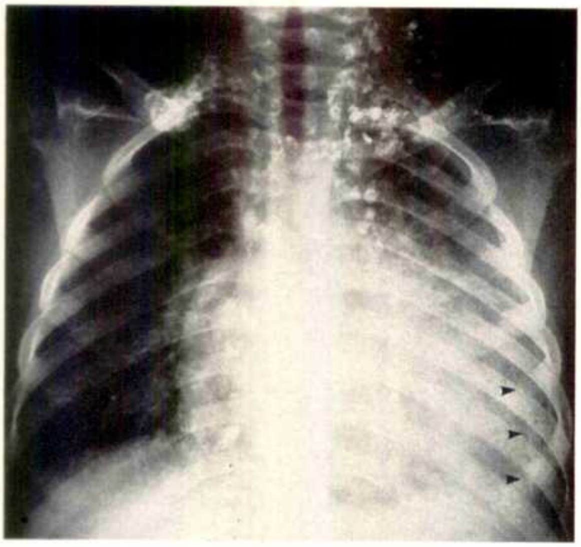

FIG. 11. *Case 3.*

At 24 hours, there is diffuse reticular opacification throughout both lungs with widespread opacification of mediastinal and supraclavicular nodes on both sides. The visceral pleural lymphatic at the left base is still filled (arrowheads).

ptosis, hypertelorism, brachycephaly, webbed neck and pulmonary valve stenosis. The latter was proved by angiography which also showed several stenoses in the peripheral pulmonary arteries on both sides. Chromosomal analysis was normal (46 XX). Her clinical and laboratory features are more fully reported elsewhere (Smith *et al.*, unpublished).

A large left pleural effusion was present. The milky fluid aspirated was rich in chylomicrons, triglycerides and lymphocytes. Excessive protein loss from the bowel was confirmed by radioisotope studies. No chyluria was found.

Lymphography was performed. The lymphatics of the lower limbs appeared normal, but those of the iliac and lumbar chains, instead of the normal parallel and longitudinal arrangement (Jackson and Kinmonth, 1974) consisted of numerous small racemose channels (Smith *et al.*, unpublished). There was also retrograde flow into lymphatics of the left renal pedicle but not actually into the kidney, and into lymphatics of the mesentery and cœliac axis (Smith *et al.*, unpublished).

The thoracic duct was well filled and the upper part looked distended (Fig. 8). There was abnormally heavy retrograde flow into supraclavicular lymphatics on both sides. Severe retrograde flow also occurred via the hila into the lymphatics of both lungs (Figs. 8 and 9). From here, there was reflux into lymphatics directly under the visceral pleura on the left side (Figs. 9 and 10) accounting for the chylothorax, and also into a lymphatic in the tracheobronchial wall on the left side (Fig. 9). No sputum was at any time available to test for chyloptysis.

At 24 hours, both lungs showed diffuse reticular opacification by the Lipiodol (Fig. 11). This went out to the periphery and was especially dense at the bases. The patient had been kept sitting up to slow the embolisation of the medium via the great veins into the lung capillaries. There was widespread opacification of mediastinal, supraclavicular and internal mammary nodes on both sides (Figs. 11 and 12).

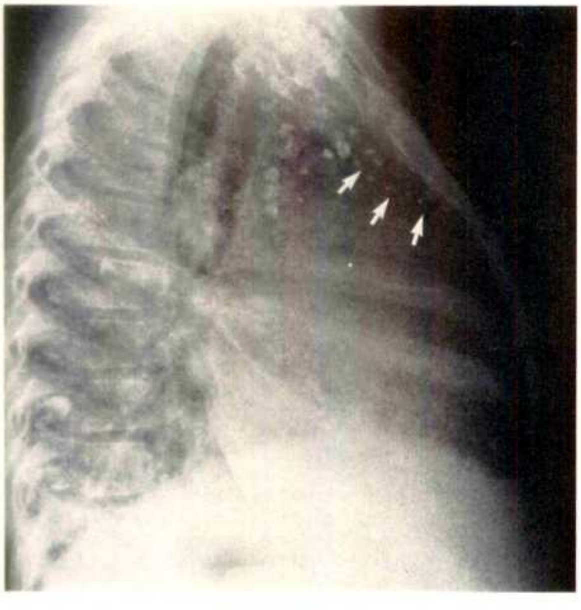

FIG. 12. *Case 3.*

Lateral view. At 24 hours, there is opacification of internal mammary nodes (arrows).

DISCUSSION

Visualization of the thoracic duct

The thoracic duct ascends on the right side of the aorta and then on the left side of the oesophagus before emptying near the confluence of the left subclavian and internal jugular veins. Its termination behaves like a sphincter (Kinmonth, 1972*a*) causing some back-up of Lipiodol in the upper part of the duct. This part is therefore regularly seen on the immediate post-infusion radiographs. For reliable filling of the lower half, however, one needs the additional aid of gravity provided by head-up tilt on a fluoroscopy table. We have not so far required additional manoeuvres (Cox and Kinmonth, 1975).

The thoracic duct seems not to be a very distensible structure; in our two cases of obstruction, although it was well filled, its width was not greatly beyond the limits of normal variation in our experience.

Drainage of thoracic lymph and of chyle (Trapnell, 1970; Warwick and Williams, 1973)

The explanation of the various lymphographic patterns lies in the lymphatic anatomy of the thorax and its normal variations (Fig. 1).

Parietal pleural lymphatics drain to the posterior intercostal and the posterior mediastinal nodes, and these in turn drain on the left side by numerous channels into the thoracic duct. The parietal pleura also drains to the internal mammary nodes which drain into the bronchomediastinal trunk on each side. The left bronchomediastinal trunk sometimes opens into the upper part of the thoracic duct but more often opens directly into the great veins.

From the pulmonary acini, some lymphatics run in the interlobular septa and then with the pulmonary veins while others run in the bronchoarterial bundles to the hilum. Opacification of the pulmonary lymphatics (Figs. 9 and 11) therefore closely resembles the pattern seen in interstitial lung disease (Heitzman, 1973). Beneath the visceral pleura is a lymphatic plexus which drains to the hilar nodes (Fig. 10) and also communicates with lymphatics of the peripheral acini.

From the lung roots, efferents ascend on the sides of the trachea and unite with efferents from the internal mammary nodes and from the mediastinal structures to form the bronchomediastinal trunk.

The left subclavian and jugular trunks draining respectively the left arm and left side of head and neck may empty either into the upper end of the thoracic duct or directly into the great veins. This variability determines whether or not an obstruction of the thoracic duct termination gives reflux into the neck and arms (Figs. 4, 8, 9 and 11).

The lymphatic drainage of the right hemithorax as well as of the right arm and right side of head and neck is into the great veins on the right side.

The lymphatic drainage of the small intestine, *i.e.* the chyle, is carried entirely by the thoracic duct. For chylothorax to occur therefore, there must be a lesion of this duct. Lesions that purely obstruct lymphatic drainage of the right hemithorax or of tributaries such as the pulmonary lymphatics may give pleural effusions but they are never chylous.

Laceration of the thoracic duct

The wall of the duct may be damaged not only by direct penetrating injury but also accidentally during surgery on neighbouring organs such as the aorta and oesophagus (Glenn *et al.*, 1975). Acute hyperextension of the spine (Glenn *et al.*, 1975) and other blunt trauma (Hyde *et al.*, 1974) can also do so.

The chyle first leaks into the mediastinum but it can then spill into the pleural cavity due to laceration of the mediastinal parietal pleura caused either by the same initial trauma or by the weight of the subsequent mediastinal collection (Higgins and Reinke, 1976). In our case, there was already a breach in the parietal pleura as evidenced by the massive haemothorax from the bleeding left subclavian vein.

If the duct is torn in the lower part of its course where it lies on the right side of the aorta, one would expect the chylothorax to be on the right side (Chavez and Conn, 1966; Hyde *et al.*, 1974). If it is torn where it lies on the left side of the oesophagus, one would expect it to be on the left (Higgins and Reinke, 1976). While this argument holds true for the spread of fluid after oesophageal rupture (Parkin, 1973), the literature on thoracic duct rupture is insufficient.

Obstruction of the thoracic duct

Surgical ligation of the thoracic duct in man and in experimental animals does not normally result in chylothorax. It is also rare in patients with enlarged nodes in the region of the duct in mediastinum or neck: this was our first case in several years' experience of staging lymphography for lymphoma.

Proof that the chylothorax in our second case was due to thoracic duct compression by the enlarged supraclavicular nodes was that it disappeared with irradiation to the nodes.

The rarity of chylous complications with thoracic duct blockage is due to the presence of collaterals between the thoracic duct and the right posterior intercostal lymphatics and to the opening up of pre-existing lymphovenous channels (Pomerantz *et al.*, 1963; Neyasaki *et al.*, 1965; Yoffey and Courtice, 1970; Warwick and Williams, 1973). For chylothorax to occur therefore, there must also be a developmental or acquired deficiency of lymphovenous communications, of left-to-right thoracic lymphatics and/or of lymphatic drainage of the right hemithorax.

If these conditions are met, chyle may leak into the pleural cavity by two routes: via the left bronchomediastinal trunk and hilar nodes to the pulmonary and visceral pleural lymphatics; and/or via the left posterior intercostal lymphatics to the parietal pleural lymphatics.

In our case of Hodgkin's disease obstructing the thoracic duct, chyle did not take the former route and the explanation may well be that the left bronchomediastinal trunk emptied (as is often the case) directly into the veins. In our case of Noonan's syndrome, there was no reflux into the intercostal lymphatics except for one on the right side (Fig. 8); for this there is no obvious explanation. The anatomy leads one to expect obstruction of the thoracic duct to give a chylous effusion purely or predominantly on the left side. We were able to find only four other reported cases (Baltaxe *et al.*, 1975; Freundlich, 1975; Diaconis *et al.*, 1976) of confirmed thoracic duct blockage in which the side of the chylothorax was stated. In one of these (Baltaxe *et al.*, 1975) the chylothorax was predominantly right sided, but in the five others including ours it was left sided.

Other points

Noonan's syndrome has many external similarities to Turner's syndrome but its chromosomal constitution is normal and pulmonary valve stenosis is common (Nora *et al.*, 1974). Four previously published cases have shown some lymphatic abnormality and in two of these lymphography showed chylous reflux into pulmonary lymphatics (Vallet *et al.*, 1972; Baltaxe *et al.*, 1975; Herzog *et al.*, 1976). Clearly therefore some kind of outlet obstruction to the thoracic duct occurs, as well as other lymphatic or lymphovenous abnormalities to account for the chylous reflux.

Our demonstration of a tracheobronchial lymphatic (Fig. 9) seems to be unique in the literature although there have been cases of chyloptysis (Löffler and Jaccard, 1954; Deuil *et al.*, 1962; Servelle *et al.*, 1968).

Chylothorax has been described in two other diseases. (i) It is common in pulmonary lymphangiomyomatosis (Kruglik *et al.*, 1976). Here there is hamartomatous proliferation of smooth muscle around pulmonary lymphatics and in mediastinal nodes, and it may be a forme-fruste of tuberose sclerosis. The chylothorax cannot result purely from compression of the pulmonary lymphatics and is probably due to the enlarged nodes compressing the thoracic duct (Monteforte and Kohnen, 1974). (ii) Lymphangectasia of the thorax with and without chylothorax has been described (Steiner *et al.*, 1969; Noonan *et al.*, 1970; Glenn *et al.*, 1975) but it remains a pathologically and anatomically ill-defined entity.

Individual cases or illustrations of lymphography in chylothorax have also been published by White and Urquart (1966), Camiel *et al.* (1971), Fuchs (1971), Weidner and Steiner (1971), Courouclis *et al.* (1974) and Grant and Levin (1974). We believe it is possible in all cases to opacify the thoracic duct up to the point of obstruction or laceration, and to show the route by which refluxing chyle reaches the visceral or parietal pleura. If there is no obvious cause of obstruction such as tumour, enlarged nodes or subclavian vein thrombosis (Diaconis *et al.*, 1976), one should then look for clinical features of a congenital or genetic disease. For instance, lymphoedema of the legs occurs frequently in Turner's syndrome and in Swyer's syndrome (Kinmonth, 1972b) and chylous complications occur in Noonan's syndrome.

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Book reviews

Biomedical Ultrasonics. By P. N. T. Wells, pp. ix+635, illus., 1977 (London, Academic Press Inc.) £24·00.

The contributions which Dr. Wells has already made to the literature on medical ultrasound are now the standard texts read by most people working within this speciality. With this new book Dr. Wells has produced a comprehensive and authorative reference work on every aspect of the subject. The text is intentionally heavily biased to a thorough discussion of the physical principles from basic sonics through the production of ultrasound; its interactions with matter and its reception. He has reviewed virtually every significant paper on the subjects covered and discusses the findings, claims and opinions of other authors in an informal, interesting and readable manner. The list of references is very complete and includes the major papers of relevance up to 1975.

As a reference book it will unquestionably be of great value to physicists and engineers, whilst the excellent sections on potential hazards should be read by all clinicians involved in the use of diagnostic—and especially therapeutic—ultrasound.

Whilst the technical sections deal with virtually every type of ultrasound apparatus ever conceived the clinical sections are also comprehensive and include a wide range of less well known uses such as neural stimulation, vestibular surgery and the ultrasonic decalcification of tissues.

The ultimate value of a reference book depends upon the ease with which one can access the information contained therein. The structure and format of this book, combined with an excellent index, enable the reader to locate information rapidly and it can therefore be very strongly recommended to all those in any way associated with the current biomedical usage of ultrasound.

H. B. MEIRE.

Nuclear Medicine—Focus on Clinical Diagnosis. By R. P. Spencer, pp. 249, illus., 1977 (Henry Kimpton, London), £9·00.

This small volume covers the clinical aspects of nuclear medicine and, as the author indicates in his preface, offers "a broad (and admittedly rapid) glimpse of the range of subjects in nuclear medicine". There is no treatment of the underlying physics, chemistry or radiopharmacy and one is referred to alternative texts for these. However, the text in general is very concise, accurate and up-to-date and achieves the goal the author has set himself admirably. The relative emphasis on imaging procedures simply parallels the work load of most departments but dynamic studies, body "compartments" and haematological aspects are all covered.

Occasionally other techniques, such as X-ray, ultrasound and endoscopic examination are ignored, which places the radioisotope techniques in isolation rather than in a clinical context. The double isotope Schilling Test described uses ^{57}Co and ^{60}Co. This latter seems a strange choice in modern times.

Another curious feature which the author feels necessary to include—despite the avowed intention of avoiding the scientific side of the subject—is a note on the radio-decay equation, in which exponential decay is explained. The author obviously feels this is a problem worthy of special attention, striking an odd note, as it is so basic to so much of nuclear medicine!

The book is produced in plastic ring binder form; some illustrations are of relatively poor quality. Nevertheless, the general text represents a notable achievement. There is a brief index.

The book certainly succeeds as the best short clinical text on the whole subject.

D. H. KEELING.

1978, *British Journal of Radiology*, *51*, 428–431

Metacarpal cortical area as an index of bone mass

By R. A. Evans, M.B., B.S., F.R.A.C.P., G. D. McDonnell, M.B., B.S. and M. Schieb, M.B., B.S., D.D.R., F.R.A.C.P., M.R.A.C.R.

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Abstract

X-rays were taken of the hands of 379 normal subjects aged from 17 to 80 years, using fine grain film. After twelvefold enlargement by an overhead projector, tracings were made of the outline of both second metacarpals and of their cortices. The total and cortical areas were measured, using a digitizer interfaced to a calculator. There was found to be a significant correlation of cortical area with total area, with different regression equations for males and females. The cortical areas were therefore corrected to a mean male-female total area (788 mm^2), using the appropriate equation. The mean total area for all males was 905 mm^2 and for females 752 mm^2. Though the cortical area was greater for males it was found that after correction for total area the cortical area for males and females aged 20–50 years was similar at 190±21 mm^2 (mean±S.D.). After the age of 50 years the corrected cortical area decreased in both sexes; by 75 there was a mean fall of 39% in females and 18% in males. The reproducibility for corrected cortical area was 2.6% for individuals and 1.5% for groups. Compared with the bone mineral analyser this technique is simpler, requires less expensive equipment and gives a better measure of bone size; compared with the simple linear measurements of cortical width it provides greater reproducibility. It is useful as a measure of bone size and bone mass, for observing the course of osteoporosis and its treatment, and for epidemiologic studies.

Many techniques have been devised for the assessment of bone mass. Of these the various radiological densitometric methods (Mack *et al.*, 1949) are now little used. The femoral trabecular index is considered of value by some (Singh *et al.*, 1972) but not by others (Khairi *et al.*, 1976) and is at best semiquantitative. Total body calcium as measured by neutron activation analysis (Cohn *et al.*, 1974) is a precise measurement but requires expensive equipment. It has the disadvantage of administering a substantial radiation dose, and its reading includes extraosseous calcium.

Measurements of the second metacarpal bone have been used for many years (Barnett and Nordin, 1960) and several indices have been devised (Barnett and Nordin, 1960; Meema and Meema, 1963; Garn *et al.*, 1967; Exton-Smith *et al.*, 1969; Gryfe *et al.*, 1971) using mid-shaft cortical width, total width and sometimes length. They all have the limitation of sampling at only one site along the cortex, and of measuring accurately to 0.25 mm at best.

Cameron and Sorenson (1963) reported the development of what has become known as the "bone mineral analyser", which gives an estimate of the mineral content of standardized sites in the right radius. This has been reported to have reproducibility (coefficient of variation) of 2.6% and 3.6% for mid-shaft and distal mass respectively (Johnston *et al.*, 1973). This high precision and relative simplicity of operation has made it a valuable research tool.

As the metacarpal measurements are inferior to the bone mineral analyser principally because of a relative crude and imprecise technique it was decided to measure the entire cortical area in order to sample a larger amount of bone and to improve the reproducibility of the method.

Method

1. Area measurements

Three hundred and seventy nine male and female controls aged 17 to 80 (hospital employees and visitors) and 20 patients with unexplained vertebral fractures underwent antero-posterior X-ray of both hands on a single fine grain film (Kodak X-M2). The image was projected onto a sheet of paper with a twelvefold enlargement by an overhead projector (3M type 297) and the outlines and internal cortical margins of both second metacarpal bones were traced. The areas in the tracings were measured using a Hewlett Packard 9864A digitizer interfaced to a Hewlett Packard 9815 calculator (used in preference to a planimeter because of the large numbers involved). The data was assembled by one worker and the randomized films were measured by another.

To determine the reproducibility of the method four normal subjects were X-rayed six times, using a different machine for each.

2. Linear measurements

These were carried out in some films for the purpose of comparison with the area measurements. The groups measured were males aged 30–40 years, females 30–40, females 60–70 and the group used to test reproducibility. Measurements were made using a plastic ruler as recommended by Morgan *et al.*, (1967), of mid-shaft total (T) and internal (M) diameter. The readings were made to the nearest 0.25 mm.

TABLE I

Area measurements expressed in mm^2 as mean ± standard deviation

Age	Total area		Cortical area		Corrected cortical area	
	Male	Female	Male	Female	Male	Female
10–20	852 ± 65 (N = 14)	715 ± 77 (N = 17)	196 ± 42	170 ± 25	190 ± 40	186 ± 20
20–30	887 ± 85 (N = 29)	683 ± 67 (N = 42)	203 ± 32	169 ± 27	193 ± 31	191 ± 22
30–40	914 ± 93 (N = 24)	740 ± 76 (N = 30)	203 ± 26	184 ± 26	191 ± 25	195 ± 22
40–50	894 ± 83 (N = 25)	716 ± 69 (N = 36)	194 ± 31	181 ± 27	184 ± 27	196 ± 24
50–60	925 ± 83 (N = 26)	728 ± 69 (N = 36)	187 ± 34	158 ± 26	173 ± 33	170 ± 24
60–70	919 ± 98 (N = 23)	754 ± 99 (N = 29)	179 ± 34	131 ± 26	166 ± 30	138 ± 24
70–80	929 ± 70 (N = 18)	743 ± 54 (N = 25)	155 ± 30	115 ± 24	140 ± 32	125 ± 23
80–90	—	690 ± 78 (N = 5)	—	119 ± 15	—	112 ± 11

3. Calculations

The mean of the left and right hands was used for the calculations. From the area measurements were calculated the total area and cortical area. In 206 subjects in whom the dominant hand could be identified, the total areas were compared in the two sides. The mid-shaft measurements were used to obtain the cortical width, and the Barnett-Nordin index (T–M)/(T).

The frequency of a diminished amount of bone was tested, as suggested by Morgan (1973), by observing the percentage of normal female subjects aged 60–70 years whose cortical area was less than two standard deviations below the mean of the females aged 30–40 years. This procedure was also carried out using the cortical width and the Barnett-Nordin index.

Results

1. Area measurements

These are shown in Table I. In the 20–30 year age group, which is regarded as being the most homogeneous, there was a significant correlation of cortical area (CA) with total area (TA). The correlating equations were for the males $CA = 113 + 0.10 \times TA$, ($r = 0.28$, $p < 0.05$) and for the females $CA = 27 + 0.21 \times TA$, ($r = 0.57$, $p < 0.001$). As the equations differed significantly ($p < 0.005$), the one appropriate to the sex was used. The cortical areas were then corrected to the mean TA of 788 mm^2 and the corrected cortical area (CAc) values are also shown in Table I. The mean CAc for the males aged 20–50 years did not differ significantly from that of the females of the same age group, though there was a just significant ($p < 0.05$) difference between the males and females aged 40–50 years. The difference was considered perhaps a chance finding, and so the males and females aged 20–50 years were regarded as a homogenous group whose CAc was 190 ± 21 mm^2 (mean ± SD); none of the six subgroups differed significantly from this. The figure shows the CAc of the controls and of patients with unexplained vertebral fractures; 80% of the latter fell below the mean minus two standard deviations of the 20–50 age group.

The mean level of the control females also fell below this value after 60 years, and the males reached it at 70 years.

The mean total area of the second metacarpal of the dominant hand in 206 subjects was 794 mm^2 and that of the non-dominant hand was 792 mm^2. The difference was not significant.

Table II shows the results of the reproducibility study; the coefficient of variation of the means of the six groups of readings was 1.5%.

TABLE II

COEFFICIENTS OF VARIATION OF THE MEANS OF FOUR SUBJECTS X-RAYED SIX TIMES

Subject	Total area	Cortical area	Corrected cortical area
1	1%	4%	3.1%
2	0.5%	2.1%	2.1%
3	1.4%	2.5%	1.7%
4	0.8%	3%	2.9%
Mean	0.9%	2.9%	2.6%

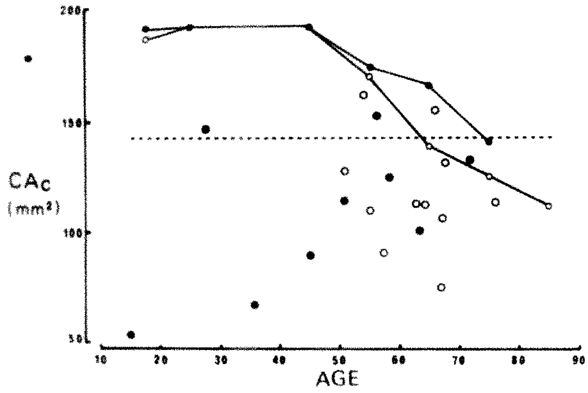

FIG. 1.

Corrected cortical area of males and females. The unbroken lines show the mean of the controls. The dotted line represents the mean less two standard deviations of the males and females aged 20–50 years. The individual points are of patients with unexplained vertebral fractures. The open circles represent females, and the closed circle males.

The frequency of low readings in the 60–70 years females was 62% using the CA, and 86% using the CAc.

2. Linear measurements

In the reproducibility study the mean coefficient of variation of the Barnett-Nordin index was 3.2% and that of cortical thickness 3.5%. The frequency of low values in the females aged 60–70 years was 65% for cortical thickness and 38% for the Barnett-Nordin index.

DISCUSSION

Measurement of the metacarpals in this manner has several advantages over other metacarpal measurements. Unlike many indices (*e.g.* Garn, Exton-Smith) it expresses a defined area and it does not make the assumption that the bone is tubular. Its precision is greater than the other measurements, and it is more effective in detecting low values.

The bone mineral analyser is at present the most promising device for widespread measurement of bone mass. Its readings are highly correlated with the ash weight of the appropriate segment of either excised bone or of bone covered by tissue remnants (Cameron *et al.*, 1968), but appropriate studies have not been made of bone surrounded by normal tissue. A comparison of metacarpal cortex measurements with ash weight has been made by Exton-Smith who measured the index T^2–M^2 in the third proximal phalanx of living subjects and found a high correlation with the ash weight of the same bone post-mortem (Exton-Smith *et al.*, 1969). So both the bone mineral analyser and metacarpal cortical measurements appear to give a good indication of the amount of bone mineral.

From the viewpoint of clinical and investigational value the important aspects are the reproducibility of the method, the variance of the site and the degree of change in the readings with age and disease. In the four subjects studied the reproducibility was 2.9% for cortical area and 2.6% for the corrected cortical area compared with 2.5 to 3.6% for the bone mineral analyser, depending upon the radial site (Johnston *et al.*, 1973). The variance of the site in this study appears to be similar to that of a bone mineral analyser study (Johnston *et al.*, 1968). The percentage decrease in bone with age is greater with corrected cortical area than with the bone mineral analyser (Johnston *et al.*, 1968). Both methods show osteoporotic patients to have a lower mean but substantial overlap with controls.

Cortical thickness measurements have been criticized on the grounds that they do not measure trabecular bone (Johnston *et al.*, 1968). However, the bone mineral analyser reading does not distinguish cortical from trabecular bone and the proximal site which has the better reproducibility, contains mostly cortical bone. There is no evidence that this measure at one or two sites in the radius is a more representative or more useful indication of skeletal mass than is the cortical area of the metacarpals. The large amount of overlap of bone mineral analyser measurements between normal and osteoporotic subjects is an indication that this purported advantage is not of practical significance.

Occasionally cortical area measurements may not be valid due to cortical striation, for example in thyrotoxic bone disease (Meema and Meema, 1973). However, bone mineral analyser measurements can also be misleading, for example in reporting an increase in bone mass in supposedly osteoporotic patients who also have osteomalacia and whose treatment includes vitamin D.

As both methods have similar variances, reproducibilities and changes with age, and as each has equivalent problems in interpretation there would appear to be no great advantage in either. Both are superior to the simpler measures of cortical thickness because of better reproducibility, and they are therefore of value in determining changes in bone mass in individuals or groups, and to observe the effects of age or different therapies for osteoporosis. The cortical measurements have the additional advantage of accurately measuring the total size of both the bone and the cortex and could therefore be of value in epidemiologic studies. The principal advantage of the cortical area measurement is that it is simple to take high quality hand X-rays, and such films are easily measured with a planimeter or mailed to a centre where a digitizer is available. This avoids the necessity to purchase a relatively expensive machine, to replace iodine sources as necessary and to have available a sufficiently trained and experienced technician to ensure adequate reproducibility.

This study has implications concerning our understanding of osteoporosis. Assuming that the ideal bone mass is indicated by the combined male-female 20–50 years corrected cortical area, a subject of any age might be considered to be osteopaenic if the value is less than two standard deviations below the mean for this group. If this is so, it can be seen from the figure that many control females over 60 years are osteopaenic, and can be expected to have a reduced threshold for bone fracture. It is therefore likely that many elderly people with vertebral fractures will not belong to a separate group of "osteoporotics" but will have bone loss normal for their age. There appears to be a second, probably heterogeneous group whose bone mass is well outside the normal range for their age.

ACKNOWLEDGMENTS

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Limitations of fibre-optic bronchoscopy under fluoroscopy in the investigation of peripheral lung lesions

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ABSTRACT

Transbronchial lung biopsy under fluoroscopic guidance was attempted in 14 patients with discrete peripheral lesions and histological evidence of pathology was obtained in five (37.7%). The difficulties and limitations of the procedure are discussed. The radiation hazard to both patient and bronchoscope are assessed. From this study it is concluded that aspiration needle biopsy is preferred in the investigation of patients with peripheral lung lesions.

The fibre-optic bronchoscope may give valuable information as to the condition of the proximal bronchial tree, but many peripheral lesions are beyond its field of vision. Transbronchial biopsy using forceps passed through the fibroscope and guided into peripheral lesions under fluoroscopy has been advocated (Levin *et al.*, 1974; Ellis, 1975; Hanson *et al.*, 1976). The present study was undertaken to evaluate such a technique and to determine the effects of radiation on the bronchoscope.

PATIENTS AND METHODS

Fourteen patients—eleven male and three female, aged 30 to 77 years with discrete peripheral lesions suggestive of bronchogenic carcinoma, were studied. The nature and size of the lesion and the pulmonary segment in which it lay were determined from recent P.A. and lateral radiographs together with tomograms (Table I).

No patient was bronchoscoped who was considered unfit for the procedure; who could not lie flat for between three quarters and one hour; or who could not cooperate with the investigator.

After fasting overnight the patients were given an intramuscular injection of 10 mg morphine and 0.6 mg of atropine and positioned on a radiography table equipped with a single plane fluoroscopic unit.

Under local anaesthesia (4% prilocaine) an Olympus BF 5 B2 fibre-optic bronchoscope was passed transnasally and the proximal bronchial tree, including the segmental bronchi of the affected lobe, inspected for tumour involvement.

In two patients the bronchoscope was wedged in a segmental bronchus of *each lobe* in turn and the successive positions recorded radiographically. These were used to estimate the distance the instrument could be advanced in each lobe (Fig. 2).

In all cases the bronchoscope was wedged in the segmental bronchus supplying the lesion and appropriate radiographs taken. Biopsy forceps were passed through the fibroscope and attempts made to guide them into the lesion by screening in supine and oblique positions which necessitated continual repositioning of the patients (Fig. 1). When the forceps were apparently in the lesion a biopsy was taken, the forceps withdrawn and the tissue sent for histological processing using the millipore technique Grech *et al.*, 1978).

If after 30 minutes it had proved impossible to reach the lesion, radiographs were taken with the forceps as near the lesion as possible.

The tip of the bronchoscope was left *in situ* and the biopsy forceps withdrawn. A fine catheter (Surgimed, Number 160, 100 cm long) was introduced into the segmental bronchus via the suction canal of the fibre-scope. A few millimetres of Dionosil Oily* were injected and when the bronchi were adequately filled A.P. and oblique bronchograms were taken (Fig. 3).

The radiation received by each patient was calculated from the records of the screening time, the number of radiographs taken and the exposure factors. In order to estimate the radiation reaching the fibrescope a tissue-equivalent phantom simulating an average chest was used. A 35 ml ionization chamber (Pitman Ltd., Type 37c) was placed within the phantom so as to simulate the position of the bronchoscope during bronchoscopy and the phantom irradiated with the average radiation dose for the series. The radiation measured in the chamber approximated to that which would reach the bronchoscope.

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*Dionosil Oily: 60% suspension of the n-propyl-ester of 3:5 diiodo 4 pyridone-N-acetic in arachis oil. Produced by Glaxo Laboratories Ltd., England.

TABLE I

PHYSICAL CHARACTERISTICS OF LESIONS, FLUOROSCOPIC EXPOSURE AND HISTOLOGY OF BIOPSIES

Case No.	Nature, size and position of lesion	Fluoroscopy	Histology of transbronchial biopsy	Histology of needle biopsy (1) or thorocotomy (2)	Final diagnosis
1	Solid, round, 4 cm in diameter in R.U.L. anterior segment	130 sec at 75kV	Lung parenchyma. No tumour seen	(1) and (2) squamous cell carcinoma	Bronchogenic carcinoma
2	Solid, round, 4.5 cm in diameter	110 sec at 75 kV	Lung parenchyma. No tumour seen	(1) Squamous cell carcinoma	Bronchogenic carcinoma
3	Rugged thick walled cavity, 6.5 cm in diameter in L.U.L. apical segment	95 sec at 75 kV	Lung parenchyma. No tumour seen	(2) Poorly differentiated carcinoma	Bronchogenic carcinoma
4	Solid, round, 2.25 cm in diameter in L.U.L. posterior segment	110 sec at 75 kV	No tissue obtained	(1) Malignant cells—typing not possible	Bronchogenic carcinoma
5	Solid, rugged 4 cm in diameter in R.U.L. apical segment	95 sec at 70 kV	Well differentiated Epidermoid carcinoma	(1) and (2) Well differentiated epidermoid carcinoma	Bronchogenic carcinoma
6	Solid, segmental, 3 cm in diameter in R.U.L. anterior segment	90 sec at 70 kV	No tissue obtained	(1) and (2) Fibrous tissue, no tumour seen	Scarring from old T.B.
7	Solid, round, 4 cm in diameter in L.U.L. posterior segment	180 sec at 70 kV	Squamous cell carcinoma	Not done	Bronchogenic carcinoma
8	Solid, elliptical, 8 cm in diameter in L.U.L. apical segment	95 sec at 65 kV	Lung parenchyma. No tumour seen	(1) No tumour seen	Bronchogenic carcinoma
9	Solid, oval, 3 × 2 cm in diameter in R.U.L. anterior segment	No records kept	Undifferentiated small cell carcinoma	Not done	Bronchogenic carcinoma
10	Solid, round, 2 cm in diameter in L.U.L. anterior segment	100 sec at 70 kV	Lung parenchyma. No tumour seen	Not done	Bronchogenic carcinoma
11	Thick walled cavity, 8 cm in diameter in R.U.L. apical segment	125 sec at 70 kV	Atypical cells suggestive of carcinoma	Not done	Lung abcess
12	Solid, round, 6 cm in diameter in R.U.L. posterior segment	No records kept	Poorly differentiated epidermoid carcinoma	Not done	Bronchogenic carcinoma
13	Solid, elliptical, 4.5 cm in diameter in L.U.L. anterior segment	105 sec at 70 kV	Lung parenchyma No tumour seen	(1) Epidermoid carcinoma	Bronchogenic carcinoma
14	Solid, round, 5 cm in diameter in R.U.L. posterior segment	120 sec	Not done	Not done	Inflammatory lesion

RESULTS

In every case the trachea, main bronchi and appropriate segmental and subsegmental bronchi were normal bronchoscopically.

Dynamic movement of the bronchial tree produces the variation in position of the bronchi seen on the radiographs. In consequence the bronchograms were considered the most reliable way of assessing the position of the bronchoscope when wedged within a segmental bronchus. We found that the instrument could not be advanced further than the second bronchial generation in the upper and middle lobes

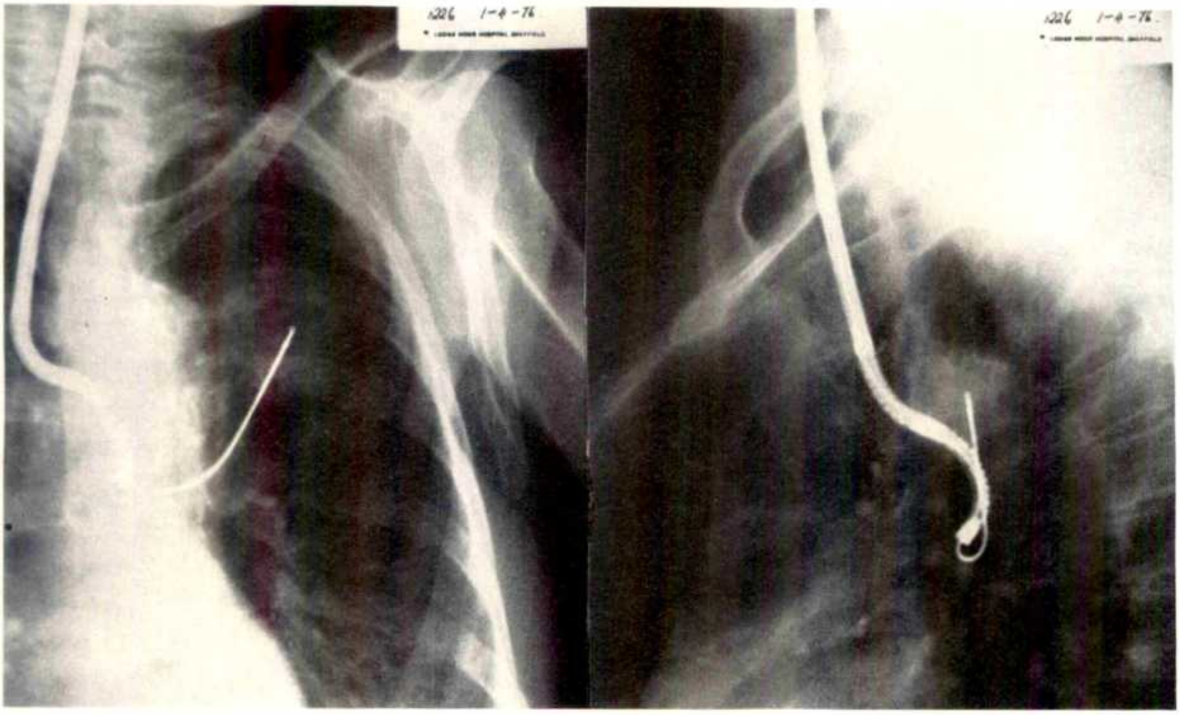

Fig. 1.

Supine and oblique view showing the bronchoscope with the biopsy forceps in the lesion (Case 7). Note that the tip of the fibre-scope has become displaced from its position in the posterior segmental bronchus of the left upper lobe.

but that in the lower lobes it wedged in the third generation. The composite line drawing (Fig. 2) was constructed from the radiographs to show the position of the bronchoscope when wedged in the most accessible bronchus of each lobe (Case 13).

In 11 cases the histology of the transbronchial biopsy showed bronchial or lung tissue. In only five was there evidence of pathology; in one (Case 11) the histology suggested bronchogenic carcinoma but the subsequent course has shown the lesion to be a lung abscess; the diagnosis of bronchogenic carcinoma was confirmed in the other four. The clinical course in the six cases where the biopsy showed normal lung tissue has been that of bronchogenic carcinoma and in four out of five other biopsies have confirmed this diagnosis. In three cases it was impossible to reach or biopsy the lesion in spite of

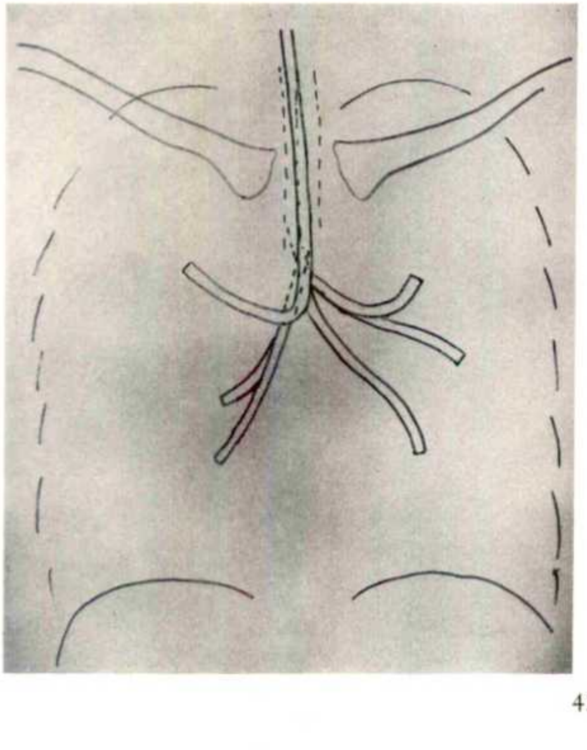

Fig. 2.

A composite line drawing constructed from the radiographs of Case 13 to show the position of the bronchoscope tip wedged in the most accessible bronchus to each lobe.

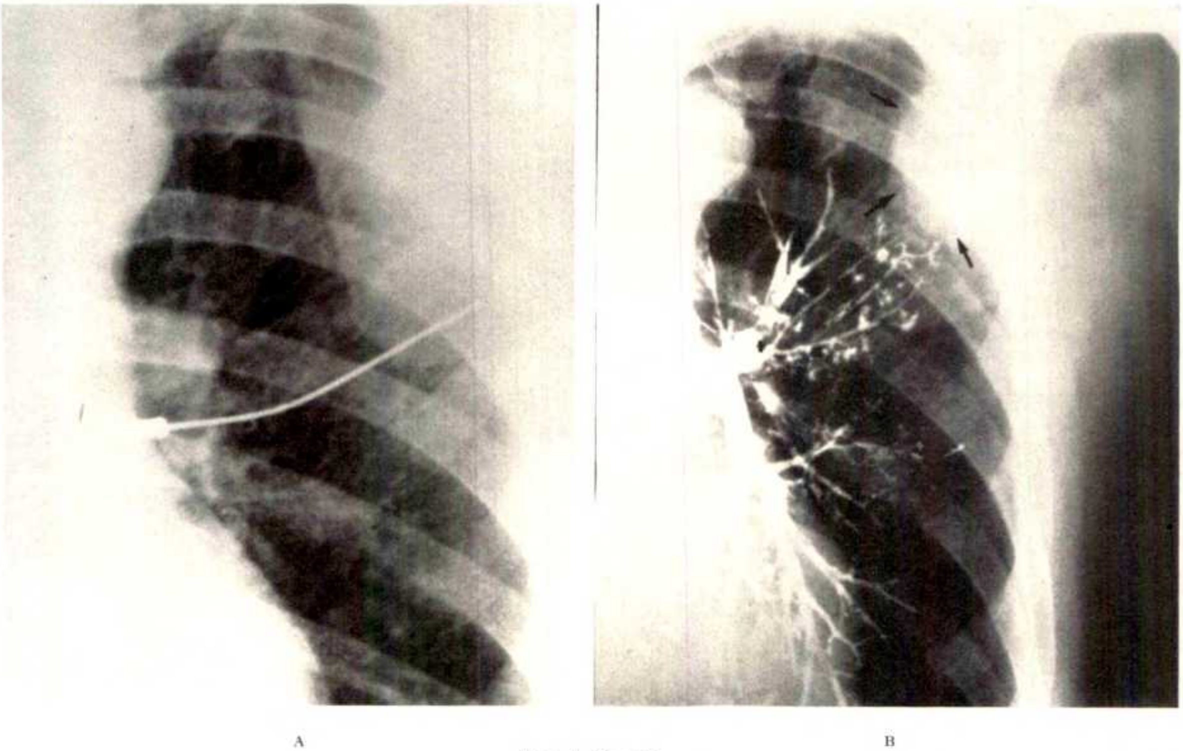

FIG. 3. *Case 2.*

(A) shows the bronchoscope wedged in the upper lobe bronchus and the biopsy forceps advanced quite peripherally but away from the lesion. (The histology of the transbronchial biopsy was only lung parenchyma).

(B) Bronchogram to outline the bronchial tree to show the tract of the biopsy forceps (A). The small curved arrow points to the tip of the bronchoscope and the three straight arrows show the lesion which was to be biopsied. The distortion of the bronchial tree might have helped in deflecting the forceps away from the lesion.

trying for 30 minutes. The histology of the transbronchial biopsy is compared in the table with the findings of percutaneous aspiration needle biopsy and/or thoracotomies in the same patients.

There were no complications from either the bronchoscopy or biopsy.

CALCULATION OF THE RADIATION REACHING THE FIBRE-OPTIC BUNDLES

The screening current of the equipment is controlled automatically by the image brightness of the intensifier (which will vary with the size of the patient) but was usually about 0.2 mA. It was calculated that the patient's skin exposure varied from 0.1 to 0.5 rad per minute screening and about 0.21 rad per radiographic exposure. The average skin exposure per patient was 2.6 rad.

From measurements with the tissue-equivalent phantom it was estimated that the radiation reaching the bronchoscope was 0.107 rad per examination. Due to the screening effect of the stainless steel coil within the fibrescope sheath the dose reaching the fibre bundles will be reduced to between 25 to 30% of this figure (0.027 rad). Any reduction in the transparency of the fibre-optic bundles will depend on the radiation dose and the length of the bundle exposed to the radiation. As the average length of fibrescope exposed during fluoroscopy was 0.19 metre the fibre bundles will be exposed to approximately 5×10^{-3} rad metres per examination.

DISCUSSION

In practice we have found it difficult to pass the tip of the instrument beyond the second or third bronchial generations, although Kovnat *et al.* (1974) using a similar instrument claimed to have entered two further generations. In time the tip becomes less flexible and its width increases due to wrinkling of the surface and both factors will tend to limit its advance. Wherever the instrument is wedged it is possible to visualize two or three further bronchial generations, but this proved inadequate to permit us to see any of the lesions studied.

At each bronchial bifurcation the advancing biopsy forceps tend to pass into the most accessible bronchus. While fluoroscopy will show the general direction of advance neither the site of bifurcation nor the correct bronchus to enter can be seen. The operator is working blindly and the difficulties are increased the greater the distance to be traversed. In the region of the lesion there may be distortion of the bronchial tree and the forceps may be deflected away from the lesion (Fig. 3). The considerable variation in bronchial diameters with respiration, movement and coughing may lead to displacement of the bronchoscope or forceps (Fig. 1). As a result of these difficulties we biopsied less than half of the lesions. The success rate might have been improved by using bi-plane or C arm fluoroscopy.

The procedure is time consuming and apart from requiring cooperation on the part of the patient may expose them to significant radiation. We have calculated that on an average the patient received 2.6 rad. Although this amount of radiation is acceptable, being less than the average exposure for a barium meal, it is not negligible considering that such patients have respiratory disease possibly requiring repeated chest radiographs.

There is also the potential damage to the fibrescope from the radiation exposure. The yellowing of glass exposed to large doses of radiation has been known for many years (Becker, 1965) and the induced change in optical density has been used for dosimetry purposes. In general, doses in the order of 10^3–10^6 rad are required to produce significant changes in thicknesses of a few millimetres. A considerable length of the fibre-optic system is exposed to radiation during most endoscopies. Ashby *et al.* (1976) have shown that the loss of light in a fibre-optic duodenoscope is dependent on the radiation dose times length of the fibre bundle exposed, and that a light loss of 45%, which made the fibre-optic bundles clinically unuseable, was produced by a dose 26.1 rad metres at 85 kV or 31.1 rad metres at 100 kV. They estimated that these changes would occur after approximately 233 examinations involving endoscopic retrograde cholangiopancreatography. Our estimations have shown that as the fibre-optic bronchoscope was exposed to 5×10^{-3} rad metres at each examination its life expectancy would be considerably greater, approximately 5000 examinations being required before the 45% loss of light occurs.

Ellis (1975) described transbronchial biopsy of peripheral lesions using the fibre-optic bronchoscope and obtained a diagnostic biopsy in 80% of cases with lesions greater than 4 cm in diameter and 58% with lesions less than 4 cm in diameter. We have been less successful in biopsying lesions ranging from 2 cm to 8 cm in diameter. In the 11 cases where a biopsy was possible we obtained a positive diagnosis in 45%.

The technique of transbronchial biopsy has to be compared with percutaneous aspiration needle biopsy under fluoroscopy in such lesions. With the needle biopsy we have had a positive diagnosis in 46 out of 50 cases (92%) (Grech *et al.*, 1978). The aspiration needle biopsy technique used has been described in detail (Grech and Clark, 1978) and has proved to be quicker, less distressing to patients and entailing much less exposure to radiation while at the same time being accompanied by no serious complications.

We conclude that in view of the technical difficulties, the radiation hazard and our histological success rate the place of transbronchial biopsy of peripheral lesions is limited in spite of fluoroscopy guidance and that percutaneous aspiration needle biopsy is to be preferred.

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A comparative survey of multi-directional tomographic units

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ABSTRACT

There are presently available in the United Kingdom six different X-ray machines capable of multi-directional tomography. A comparative assessment of the units and their performance was made with particular emphasis on (i) the suitability of the units as general purpose instruments, for routine radiography and the wide range of tomographic examinations required in a district general hospital; (ii) the performance of the most sophisticated machines, in the demonstration of small ear structures. The quality of the pictures obtained, the radiation dose to the patient and ease of operation by specialist or inexperienced radiographers were considered.

Hypocycloidal and tri-spiral tube movements gave the most uniform blurring, free from "streaking" and false images, and hence were the best for thin section ear tomography. There was no significant difference in the quality of the image produced by the Polytome and Stratomatic. In this investigation the Polytome produced a thinner section (0.6 mm) than the Stratomatic (0.9 mm). These complicated tube movements offer significant advantages only for tomography of the base of skull and face, and the authors believe that unless there is a particular interest or demand for special examinations of this region, a unit with circular or elliptical combined with linear tube movement is adequate. Press-button selection of movements and angles and change to conventional radiography are desirable on such a unit but it is difficult to justify a fully-automated system for any tomographic unit.

Although multi-directional tomography has been possible since the 1930's it was not until about 15 years ago that advances in technology led to machines with a complicated tube movement becoming freely available. These units were often purchased with no clear idea of the values and limitations or even appropriate applications of multi-directional tomography. An unfortunate new term "polytomography" was introduced, which seemed to imply a different and superior type of investigation. As du Boulay (1969) pointed out, the only advantage of multi-directional movement is an even blurring without streaking. With linear tomography it is possible to obtain sections as thin if not thinner than with a multi-directional movement.

Nevertheless, it is in the investigation of ear abnormalities that the greatest refinements and developments of uncomputerized tomography have most value. The authors' experience of ear tomography was used as a basis for a comparative survey of the performance of available tomographic units in this field. Very few such studies have been made and we know of only one attempt to assess objectively the ability of two different machines to demonstrate small ear structures (Wilbrand and Bergstrom, 1975) although various tomographic test objects have been constructed and used to measure layer thickness and definition (Wilbrand, 1975; Littleton, 1976a). Littleton's book gives a most comprehensive account of the practical aspects of multi-directional tomography.

There now seems to be a trend towards the purchase of more versatile tomographic units with simpler tube movements which adapt easily to conventional radiography. It was therefore decided to assess the versatility of all multi-directional tomographic units and hence their suitability as general purpose machines in a district general hospital. As well as making subjective assessments of the quality of the radiographs obtained, it was decided to compare the cost of the basic unit, the space occupied, and ease of operation. The radiation dose to the eyes during tomography of the petrous temporal bone was also measured.

METHODS

There are presently available in the United Kingdom six uncomputerized tomographic units capable of multi-directional as well as linear tube movement. These are made by five different companies (Table I). A Polytome and a Maxitome are in use in the authors' departments and one of us has personal experience of the Multiplanigraph. The other machines were assessed during visits to other departments and discussion with the staff using them. In most cases more than one machine of each particular type was investigated. It was difficult to obtain figures for the number of different tomographic examinations performed on each unit and this aspect is not considered in this survey.

A standard skull phantom was used throughout. Although the vagaries of different machines made it difficult, all radiographic factors were kept constant as far as possible. These included exposure, field size, film-screen combination and focal spot size. Coronal sections through the middle and inner ears at the level of the oval window were compared.

For the three most sophisticated units (the Maxitome, Polytome, and Stratomatic), special views were taken of the vestibular aqueduct. Wilbrand *et al.* (1974) have described the variations in the course of this structure and the projection required to

TABLE I

Multi-directional tomographic units available in Great Britain

Unit and manufacturer	Floor space	Cost of basic unit
Polytome U1 Philips U3	2600 × 3710 mm	£20670 £43735
B.T.S.2 Philips	2140 × 3700 mm	£22409
Multiplanigraph 2 Siemens	2762 × 2900 mm	£18275
Stratomatic H G.C.E. U	1976 × 3400 mm	£31370 £47070
Plurigraph G.E.C. (Picker)	1880 × 2960 mm	£23553
Maxitome I.G.E.	2819 × 3352 mm	£39460

The prices quoted are for the basic unit only and are the most recent supplied to us by the manufacturers (1.7.77).

The Polystratix (C.G.R.) has been discontinued and its replacement, the Exastratix, although now available, has not yet to our knowledge been installed anywhere in this country. A new machine, the Optiplanimat (Siemens) capable of tri- and five-spiral movement is similarly not yet installed in this country. Other machines, mostly of Italian or Japanese manufacture, are available on the world market, but we believe that the above list comprises all multi-directional tomographic machines currently available and in use in this country.

demonstrate it. We found that 10 deg. off true lateral showed the aqueduct best on our phantom skull and a template was made to reproduce the position. A tomographic test object using 1 mm metal balls spaced 5–10 mm apart, as described by Wilbrand (1975) was constructed and used to measure the layer thickness produced by these machines. The method and means of calculating layer thickness are fully described in Wilbrand's paper.

Eye dose measurements were made with thermoluminescent discs placed on the "cornea" of the phantom, as we found that these readings were almost identical to those obtained by placing the discs on the eyelids of patients. The measurements were repeated with lead shields covering the eyes and the effect of the shields on the quality of the image was also judged.

Results

The cost of these machines, shown in Table I, is for the basic unit without generator, X-ray tube or special accessories; the actual purchasing price would consequently be considerably higher. It seems that these prices fluctuate widely. The space required showed no startling variations; the more sophisticated units requiring slightly more floor space than the simpler ones.

TABLE II

Radiation dose to the unprotected eye during petrous tomography in the A.P. position. Coronal sections at the level of the oval window using a small field and a standard rare earth screen film system. Dose per exposure.

Unit	Movement used	kV	Dose (average) in millirads
Polytome	Hypocycloid	75	150
Stratomatic	Tri-spiral	65	230
Maxitome	Figure of eight	55	530
B.T.S.2	Ellipse 36/18 deg.	70	550
Multiplanigraph	Ellipse 40/30 deg.	65	350
Plurigraph	Circular 30 deg.	82	100

Radiation dose to the eye

In the antero-posterior (A.P.) position of the subject, the radiation dose to the unprotected cornea during ear tomography was high, but became much reduced when lead eye shields were used or when the patient was in the postero-anterior (P.A.) position. The dosage from different types of machine varied considerably (Table II). Using a movement which gives a thicker section and a shorter exposure time did not reduce the eye dose. In some cases, notably the Maxitome, it was in fact much higher. Details of the dosages obtained and methods used have been given in a previous paper (Ashley, 1977).

Tube movement

The types of tube movement of which these machines are capable are shown in Table III. All will perform linear tomographic movements with choice of layer thickness. Most will do a reasonable selection of circular or elliptical movements, although for reasons given below we do not think that these selections are adjusted to give sections of the most useful thickness in many cases. The Maxitome is somewhat different in its mode of operation using various parts of a figure of 8 or pseudosinusoidal arc. In theory a whole variety of examinations is possible, but in practice use of the centre X results in undesirable cross streaking, and in our opinion, the only useful movements are linear and one or both ends of the 8, to give thick and thin sections respectively.

TABLE III

Unit	Manufacturer	Movements available (deg.)
Polytome	Philips	Hypocycloidal 48 Circular 0–20, 29, 36 Elliptical 40 in any direction Linear 0–50 in any direction
Stratomatic	C.G.R.	Tri-spiral 45 max. 12 min Circular 0–45 Linear 0–45 in any direction
Maxitome	I.G.E.	Figure of eight Any segment of figure of eight arc Longitudinal linear 10, 20, 40 Transverse linear 20
B.T.S.2	Philips	Elliptical 5, 8, 36 Longitudinal linear 15, 30
Multiplanigraph	Siemens	Circular 5.5 Elliptical 40 Longitudinal linear 8, 30
Plurigraph	Picker	Circular 10, 30 Elliptical 40 Longitudinal linear 6, 20, 30 Transverse linear 20

General tomography

The three simplest units, the Multiplanigraph, Plurigraph, and B.T.S. 2 offer a similar selection of tube movements (Table III). This selection is a little more comprehensive on the Plurigraph than on the other two. A comparison of coronal section ear tomograms using the largest angle circular and elliptical movement showed little difference in the quality of the radiographs obtained although in our limited investigations those obtained from the Plurigraph showed slightly reduced quality.

The Multiplanigraph has a column mounted X-ray tube and this can be used for radiography in the erect position. The Plurigraph and B.T.S.2 use ceiling suspension which allows slightly better access to the patient and also complete removal of the tube from the area of the table. The tube of the B.T.S.2 can also be swivelled for horizontal-beam radiography across the table. All three units offer easy patient positioning by utilization of a floating table top. All three have push-button selection of mode (between conventional radiography and tomography) and of exposure angle. Angulation of the X-ray tube, however, is limited to ±20 deg. unless the connecting rod is uncoupled.

Of the specialized units, the Maxitome has features similar to those of the simpler units for conventional radiography. The Stratomatic, although employing the same mechanical arrangement for both modes, can have its tube angled only 25 deg. and this is controlled from the console. The Polytome is the least adaptable for other modes of radiography as different cassette trays are necessary which are not conveniently changed. Table movement on the Polytome is in a longitudinal direction only whereas the other two each have a floating table top.

Use of a multi-layered cassette may be an advantage in many situations, particularly chest tomography, but also in ear tomography to reduce the radiation dose to the eyes. This facility is available with all the machines described except for the Maxitome.

Special tomography

The current Polytome U1 retains the original method of selecting the tomographic movement by changing the "gear" on the main drive disc. The Polytome U3 has automatic push-button selection of tomographic movement which brings it into line with the Stratomatic and Maxitome. In addition all three offer automatic beam collimation and cassette positioning for multiple exposures. These features certainly speed up the examination when many tomographic sections are required, especially if as on the Stratomatic and Polytome U3 it is possible to programme a series of tomographic levels and the interval between them. If such a facility is available a suitable X-ray tube with good loading characteristics is necessary to withstand heavy serial exposures on fine focus. The large water-cooled tube on the Stratomatic is admirable in this respect. When non-standard collimation of the beam is required, as for the small and variously shaped field sizes necessary for ear tomography, automatic collimation is a nuisance. The Maxitome is particularly difficult as the manual collimation selector button has to be depressed each time a cassette is changed and single exposures used on each film.

The Polytome is the only unit on which it is possible to angle the cassette for inclined plane tomography, as in axial tomography of the orbits (Lloyd, 1975). This is achieved by using the so-called enlargement tray, which gives a magnification factor of 1.6. By its unique system of constant geometry the Polytome offers a constant magnification factor throughout its range of layer heights. The

Stratomatic and Maxitome utilize a constant table height with variable fulcrum height and therefore have a variable magnification factor which increases as the fulcrum height increases. A variation in tomographic angle also occurs as the fulcrum height is changed. It is sometimes useful, for instance in tomography of the larynx, to be able to change the filtration on the tube. This is easily accomplished on the Polytome but not on the Maxitome or Stratomatic.

As described previously an attempt was made to compare the performance of the three most sophisticated units for ear tomography. The same cassette and a uniform field size were used throughout. Focal spot size on the Polytome was 0.3 mm and on the Stratomatics and Maxitomes 0.6 mm, as quoted by the manufacturers. We did not attempt to check these figures and there may in fact be considerable variation from them (Jensen, 1969). The Polytomes were used with the grid removed as is standard practice in most centres. The grid could be removed from the Stratomatic only with difficulty and the resultant radiographs were in any case inferior to those obtained with the grid in position. The grid on the Maxitome cannot be removed.

Layer thickness and definition

Using the tomographic test object we obtained the following layer thickness measurements: Polytome 0.6 mm, Stratomatic 0.9 mm, Maxitome 1.00 mm (Table IV). There was felt to be little difference in the quality of the coronal section ear tomograms, although these were better than the sections obtained with the elliptical movement of the simpler machines. The pictures produced by the Stratomatic were considered to have the best definition by several observers. The Maxitome pictures had the poorest definition and some cross-streaking could be identified.

The effect of 1 mm lead eye shields on the coronal section radiographs was least noticeable with the Polytome. No change of exposure factors was necessary and only faint residual shadows could be discerned which did not significantly affect the visibility of ear structures. It was necessary with the other two units to increase the exposure by 5 kV. The Stratomatic produced circular shadows and the Maxitome pronounced triangular ones. This combined with the large radiation dose delivered by the Maxitome, would seem to indicate that ear tomography should only be performed in the P.A. position on this machine.

TABLE IV

Results of layer thickness measurement using a Tomographic Test Object

Movement	Unit	Layer thickness
Hypocycloidal	Polytome 1 Polytome 2	0.62 mm 0.63 mm
Tri-spiral	Stratomatic	0.91 mm
Figure of eight	Maxitome 1 Maxitome 2	1.01 mm 0.92 mm

The vestibular aqueduct, including the isthmus, was demonstrated at each attempt with the Polytomes. However, we were unable to identify it using the Stratomatic or Maxitomes although an entirely comparable series of sections at 1 mm intervals was obtained.

Discussion

There is still a tendency to think of "tomograms" as a special investigation, although conventional tomography, unlike computerized tomography, will rarely demonstrate anything that cannot be seen on plain radiographs. The increasing use of tomography, especially with contrast investigations, means that in future conventional tomography should be used mainly as an adjunct to routine projections in the initial radiological investigation. The increasing availability of units which can be used for a wide range of routine examinations and have "push-button" conversion to tomography readily facilitates this approach. This is why we consider versatility so important in the ideal type of unit for a district general hospital which has perhaps four or five radiographic rooms.

The exception to these generalizations is in the investigation of lesions at the base of the skull where sophisticated multi-directional tomography has definite advantages. In the demonstration of small bony structures, such as the auditory ossicles or vestibular aqueduct, the best multi-directional tomographic units are capable of resolution to 0.2–0.3 mm. Computerized tomographic units are limited to the resolving capabilities of the computer matrix and the image display of the cathode ray tube: a gross capability of approximately 1.5 mm (Littleton, 1976b). In the investigation of lesions at the skull base the two types of tomography are to some degree complementary, CT showing the extent of a soft tissue lesion and multi-directional tomography the degree of bone destruction.

In the United Kingdom radiologists are rarely asked to demonstrate the vestibular aqueduct, oval window or even the full extent of a cholesteatoma.

Although linear tomography is unsuitable for ears and sinuses a 12 or 15 deg. circular movement gives a very satisfactory demonstration of lesions and structures in this region (Lloyd and Wylie, 1971). The thicker sections obtained are in some ways easier to intrepret and the main disadvantage of the circular movement, namely the creation of prominent false shadows, does not seem to be a problem. Unfortunately an arc such as this is not available on any of the simple machines (Table III).

We believe that unless there is a demand for or a special interest in the investigation of lesions of skull base, eyes or ears, tomography using linear or circular movement is adequate. Variations on these simple movements seem to offer no significant advantages although the elliptical is perhaps a useful compromise. Table V summarizes what we believe to be the required features of a general purpose unit which can be fully utilized for a wide range of standard procedures where "instant" tomography may be helpful. The intravenous pyelogram is the most obvious example; not only can a few tomographic sections be done when the calyceal patterns are obscured but an angled bladder view can also be obtained by push-button control. We considered the B.T.S.2 was the easiest unit to use and the most versatile for conventional radiography.

The radiation dose to the eyes delivered by different machines varied greatly, being particularly high in the case of the Maxitome and the B.T.S.2. We cannot account for these differences although removal of the grid would cause some dose reduction with the Polytome.

Our preferences for equipment and tomographic movement for special ear tomography are inevitably biased by greater experience with the Polytome U1 than any other machine. However, we feel that a selection of labelled lead diaphragms with apertures each giving the field size and shape required for a particular investigation is the simplest and most satisfactory form of collimation. Similarly, automatic cassette positioning for multiple exposures on one film, is no quicker than the hand-operated system in conjunction with an agile radiographer. Although the automated system of the Stratomatic is better than that of the Maxitome, we do not think that the added cost and complexity of automated systems justifies their small labour-saving advantages.

TABLE V

FEATURES CONSIDERED DESIRABLE IN A GENERAL PURPOSE TOMOGRAPHIC UNIT

Simple Bucky table
General purpose tube mount
Press-button movement and angle selection and change to conventional radiography
Floating table top
Ability to use multi-layered cassettes
Three-phase generator
Tube—High speed anode with 0.6 mm and 1.2 mm focal spot
Movements—Linear 10, 20, 30, 40 deg.
Circular (or elliptical) 12, 30 deg.

The results of our layer thickness measurements are similar to those obtained by Wilbrand although we found a greater difference between the Polytome and Stratomatic. The layer thickness measurement for the Maxitome although more than the other two was less than that obtained by Littleton (1976a). These results are dependent on a large number of variables and are only applicable to the tomographic and film screen systems used. However, our consistent ability to demonstrate the vestibular aqueduct with the Polytome but not with the other two machines would seem to depend on this difference in layer thickness. For a more complete review of the significance of layer thickness and its measurement the works of Wilbrand (1975), Littleton (1976), or Stieve (1972) should be consulted. We have unfortunately had no chance to assess the Optiplanimat which uses a tri- or five-spiral movement and apparently gives a good result concerning layer thickness (Wilbrand, personal communication).

The limiting factor in the resolution of fine detail seems to be the recording system, and the choice of a good cassette and film screen combination is probably as important as the size of the focal spot or choice of hypocycloidal or spiral movement, as long as the tomographic plane is stable and homogeneous.

CONCLUSIONS

Many comparative aspects of this survey are based on subjective assessments and personal preferences and as such are of limited value. A factor not considered and one which greatly influences any prospective purchase is the standard of after-sales service of the company concerned. Although much of the information given above may be obtained from the appropriate brochures, we feel that a critical assessment of the capabilities of these machines together with objective measurements of layer thickness and radiation dose permit the following conclusions:

A. General tomography and radiography

1. The Multiplanigraph, Plurigraph and, B.T.S.2 are the most suitable machines. They are similarly priced and have a similar choice of tube movement. We found the B.T.S.2 the easiest to operate, but it did produce the most radiation to the eyes.

2. The elliptical and circular movements can produce adequate tomograms of the ear. Expansion of the internal auditory meatus or attic erosion by a cholesteatoma can be satisfactorily demonstrated.

3. The specialized units are less suitable for general work. The most unsuitable and least adaptable is the Polytome U1 which is the only one in the same price range as the three simple units.

B. Special tomography

1. The Polytome U1, although "old-fashioned" in its mode of operation, is at the moment almost half the price of the other two specialized units. In our opinion the ability to do inclined plane tomography is very valuable and our box of home-made lead diaphragms the best system of beam collimation for tomography of the skull base.

2. In this investigation the Polytome consistently produced a thinner section than the Stratomatic and Maxitome. This is not necessarily an advantage and several independent observers considered that the coronal section ear tomograms produced by the Stratomatics were the best. However we can only attribute our consistent ability to demonstrate the vestibular aqueduct with the Polytome alone to this difference in section thickness.

3. The Maxitome, besides giving the largest radiation dose to the eyes during ear tomography, has several design disadvantages; the inability to use a multi-layered cassette and difficulties with non-standard beam-collimation in particular. The figure of 8 movement has linear characteristics and is inferior to the spiral or hypocycloidal for tomography of the skull base.

4. Although we feel that full automation is not justified for tomography as it is practised in the United Kingdom, nevertheless the Stratomatic has a well-designed system which allows a large number of rapid exposures with the minimum of effort.

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Book review

Monographie des annales de radiologie. 14. La myélographie opaque. By M. Bocher, M. Garnier, J. F. Magoyer and P. Buffard, pp. 88, illus., 1977 (L'Expansion Scientifique, Française, Paris) F.100.

Since the introduction of metrizamide, oil contrast myelography has become a method with a declining application. Many excellent texts have been devoted to the simple procedure, interpretation of pathological appearances and complications. This monograph in French adequately covers the subject and is well illustrated, but it adds nothing to the available English texts.

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Topographic relation between the myocardial uptake of radiothallium and left ventricular kinetics in myocardial infarction

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ABSTRACT

Myocardial images with thallium 201 are recorded on a computer with the ECG tracing and the cardiac cycle divided into 16 consecutive images. The patients then receive $^{99}Tc^{m}$ albumin for first pass and a subsequent ECG gated series for comparison with the myocardial studies.

These images can be superimposed and allow the topographic relationships of thallium uptake and ventricular contractility as reflected by the blood pool, to be seen. Quantitative parameters such as ejection fraction and stroke volume are also obtained. Examples in clinical practice are given.

By marking myocardium and cardiac blood pool, and recording their movements by means of a multigating technique, it is possible to determine the relationship between the degree of myocardial uptake of potassium-like isotopes and the value of the ventricular kinetics.

Up to July, 1976 a total of 240 patients underwent nuclear dynamic studies of the heart, 90 examined by combining both approaches. Abnormal cases are listed in Table I. Most of these had myocardial infarctions. This is due to the particular interest of cardiologists for this non-invasive way of assessing overall and regional functional value of the left myocardium in coronary artery disease.

The procedure we have been using is as follows: thallium 201 is first administered intravenously to the patient (2 mci). Thirty minutes later, images of the heart are recorded using an Anger camera (Phogamma LFOV) connected to a data processing system (Informatek). The views recorded are generally the frontal and left anterior oblique, plus sometimes the left lateral one, according to the clinical problem. Multigating technique spans the cardiac cycle through 16 consecutive sequences. Series of sequences are triggered by the R wave of the ECG. Two or three hundred cycles are summed to obtain good counts statistics for each sequential frame (Adam *et al.*, 1974; Agress *et al.*, 1976; Alpert *et al.*, 1974; 1976; Geffers *et al.*, 1976; Green *et al.*, 1975).

The data are stored in a buffer memory. The analogue pictures are registered on a radiographic film for immediate control and gross evaluation.

After having completed the last view, the patient is injected with 15 mci of $^{99}Tc^{m}$ serum-albumin without changing his position relative to the detector. The first passage of the radioactive bolus is recorded. Then 16 gated views of the blood pool are taken; here again, analogue and processed data are obtained.

The data can be displayed in various ways on a TV screen. The 16 sequential frames covering the whole cardiac cycle can be presented either separately for myocardium and cardiac blood pool, or superimposed. A first approach of the study is performed by grouping on the same view end-diastolic and end-systolic frames from both the myocardium and the cavities (Fig. 1A). More detailed analysis is made possible by displaying, at a high rate, the 16 frames on the TV screen. It is often better to replace the images of the cavities by isocount lines for a well chosen level of activity in order to represent the outlines of the heart chambers.

The series of isocount lines from diastole to systole can be superimposed and compared with the myocardial uptake of thallium on the same figure (Fig. 1B).

In a normal case the parallelism of the lines, with approximately the same thickness of the bundle

TABLE I

Total number of examinations (November, 1976)	286 (237 patients)
Double tracer studies (myocardium + blood pool)	92 (87 patients)
—Normals	10
—Angina	5
—Infarcts	53
—Valvular diseases	8
—Miscellaneous	11

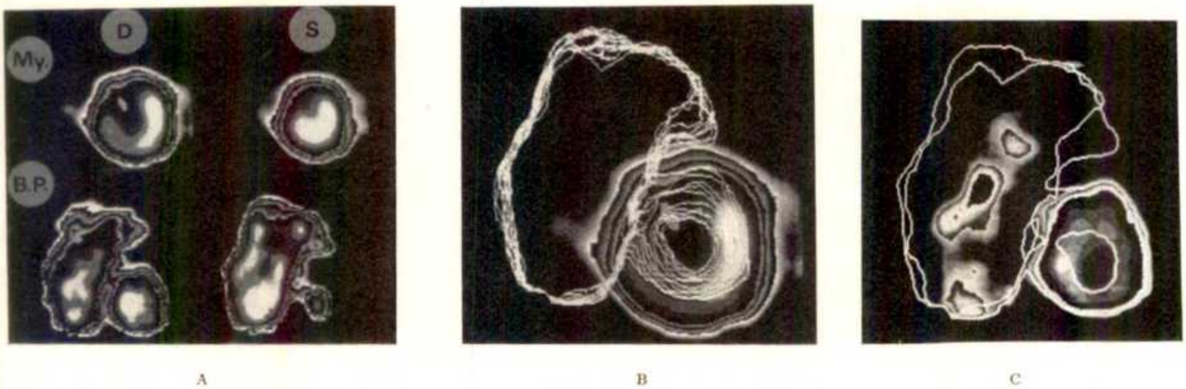

Fig. 1.

Normal myocardial and blood pool dynamic images in LAO view. (A) End diastolic (D) and end systolic (S) patterns of myocardium (My) and blood pool (BP) selected from a series of 16 frames spanning the whole cardiac cycle, at equilibrium. (Black and white photographs of the computer TV screen displaying the rate of radioactivity in a color scale. This decreases from the red white, reproduced here in white in the center, to the blue represented here by the light grey at the periphery). Homogeneous distribution of thallium reflects homogeneous perfusion. Comparison of diastolic and systolic frames of myocardium reflects a synergic and good contraction. The same holds for BP images.

(B) Sequential isocount lines of blood pool from diastole (external line) to systole (internal line) superimposed on the diastolic myocardial image taken in exactly the same position. Note the good parallelism of lines reflecting the homogeneity of the LV wall motion.

(C) Distribution of the point diastole to systole difference in blood pool counting (equivalent stroke volume), giving a functional image here in grey scale. Isocount diastolic and systolic lines are superimposed.

around the left ventricle, evidences the synchronous movement of every portion of the wall.

Another way to image the functional value of the left ventricle is to compute point by point the value of the equivalent of the ejection fraction or the diastole to systole counting difference (Itti *et al.*, 1969; Kaihara *et al.*, 1969; Luig *et al.*, 1974; Meyer *et al.*, 1974). This resulting functional image is compared with the uptake of thallium in the myocardium. According to the probability that the distribution of the uptake of thallium by the heart parallels the regional perfusion of the muscle, one could suppose that normally radioactive areas correspond exactly with the functional parts of the wall and that, conversely areas of decreased uptake are hypofunctional or even dyskinetic. Our purpose was to test this hypothesis as clearly as possible by the combined study of the muscle and its function. Quantitatively the ejection fraction is determined from the quantities of radioactivity in the regions of interest (whole ventricle or parts of it) at end diastole and end systole. Volume equivalent curves are traced from the counting rate versus time along the cycle. Alternatively the total ejection fraction can be calculated cycle by cycle from the recorded curve of the first passage in the left ventricle.

Thus it is possible to accumulate two types of data: on the one hand the topographic relationship of the areas of concentration of thallium and contractility reflected by the motion of the radioactive blood pool, and on the other hand, quantitative values of parameters such as variation of the left ventricular volume, stroke volume, time of ejection, etc. and relative values of these in different parts of the chamber.

Figures 2 and 3 illustrate two cases of myocardial infarction which were apparently very different from the clinical assessment. The first one was a 57-year-old patient with clinical and ECG signs of anterior infarction. The nuclear dynamic study was performed after infarction. The end-diastolic myocardial LAO view (Fig. 2A) reveals an extensive hypoactive area in the antero septo-apical wall. The LAO view of the cavities (Fig. 2B) shows a persistent and high activity, *i.e.* a stagnant blood pool in the area of poor uptake of thallium. Superimposition shows (Fig. 2C) the isocount lines separated only on the most radioactive portion of myocardium. On Fig. 2C, end systolic and diastolic contours are superimposed on the distribution of the "stroke volume" calculated point by point; the brighter the point, the higher the value. From these images, one can appreciate the mobility of the ventricular wall and the extent of its akinetic part. The ejection fraction is best near the left lateral wall. Near the apex it was found lower than 0.10, instead of 0.40 to 0.50 in the mobile zone. The value for the whole ventricle was 0.15.

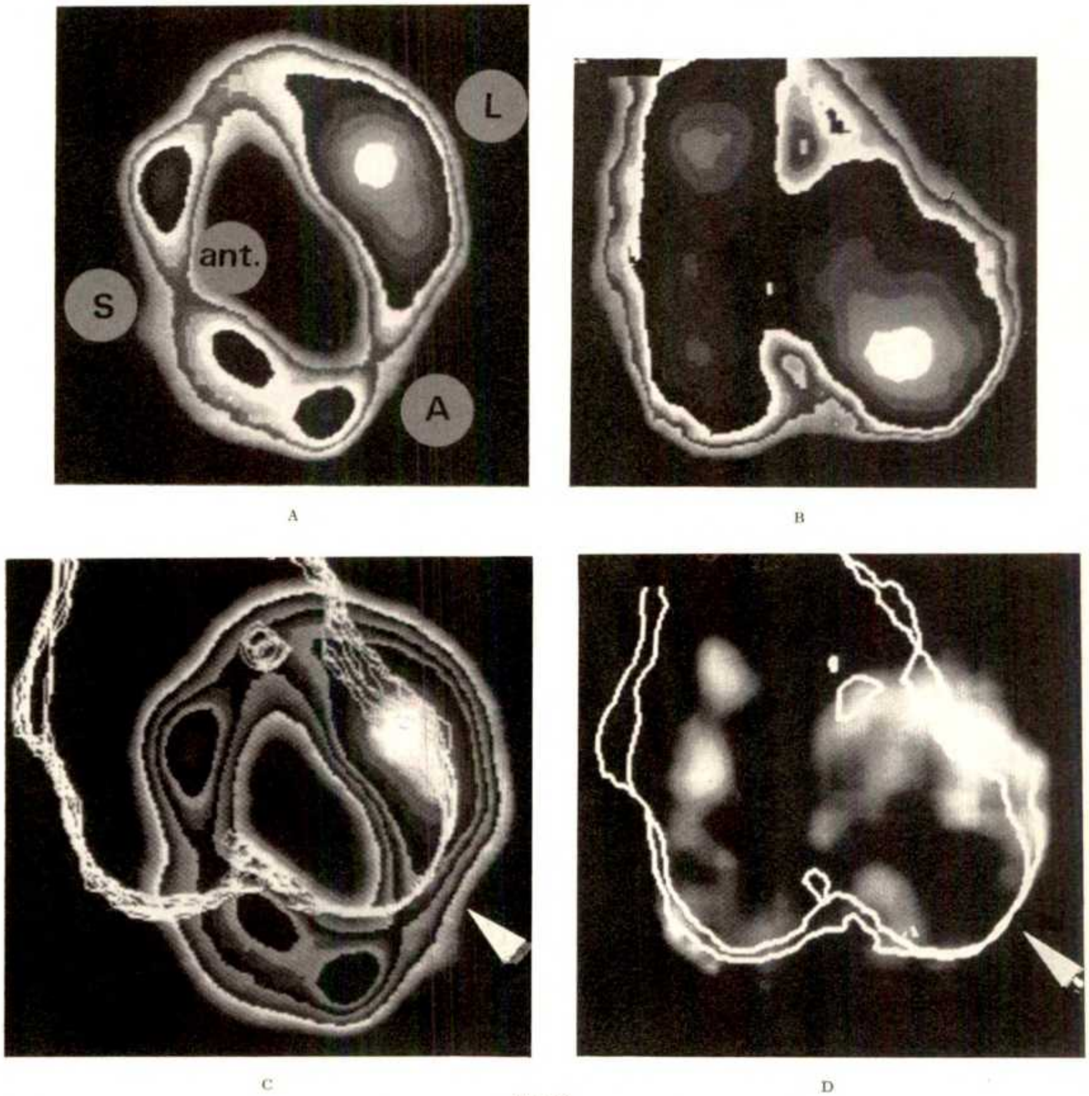

FIG. 2.

(A) Diastolic frame of left myocardium (LAO) view demonstrating a large defect on the anterior (ant.), septal (S) and apical (A) segments due to a large myocardial infarction. The uptake of thallium is normal on the lateral wall (L).

(B) Diastolic frame (in grey scale displayed) showing a dilated left ventricle.

(C) Diastolic frame of myocardium and superimposed isocount lines of the blood pool from diastole to systole. Note the topographic correspondence between the thallium uptake defect and area of akinesia (isocount lines stuck together reflecting the loss of wall motion).

(D) Functional image ("stroke volume") in grey scale, the two isocount lines representing diastolic and systolic contours are superimposed.

The second case involved a very athletic 27-year-old man, who presented with symptoms of coronary artery disease three months before our dynamic studies. At this time, all the examinations, including coronary arteriography, were normal, except for a myocardial scan showing a decreased uptake of thallium in the anterolateral wall. Three months later he developed a limited infarct in this region as confirmed by clinical, ECG and scan findings. The end diastolic and end systolic frontal images of the myocardium (Fig. 3A) reveal a thick inferior myocardial wall, but a decreased concentration of thallium in the antero-lateral wall, with a defect clearly seen on the end diastolic image. The most significant

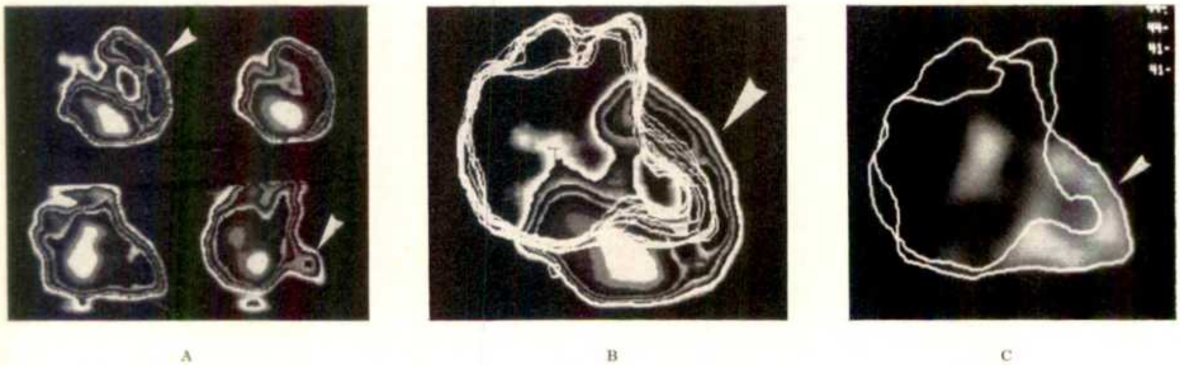

FIG. 3.

Limited antero-lateral infarction with local asynergy of wall motion. (A) *Top*: diastolic and systolic myocardial frames in anterior view. Note the high activity of the thickened inferior wall in this athletic young man. Limited defect of thallium uptake in the lateral wall, and hypo-activity in the neighbouring area. *Below:* Blood pool frames: an expansion is visible as an angle at the systolic time.

(B) Superimposition of isocount lines and myocardium shows the excellent correspondence between the local abnormality in the wall motion and the thallium defect.

(C) Superimposition of stroke volume distribution (grey scale) and extreme isocount lines. Here again, the decreased regional left ventricular function is shown by both displays.

blood pool picture is the end-systolic one with an angle on the left lateral edge. The sequential isocount lines describing the left ventricular motion superimposed on the myocardium (Fig. 3B) illustrate the close relationship between systolic expansion and low myocardial perfusion. Also (Fig. 3C) the systolic expansion corresponds to the part of the ventricle where the ejection fraction is the lowest. The mean ejection fraction for the whole left ventricle was 0.50.

A second ventriculography performed at this time confirmed the presence of a limited hypokinetic area.

The nuclear medicine procedure combining multigated myocardial and blood pool studies allows good assessment of the topographic relations between thallium uptake and ventricular function. This is particularly clear in localized myocardial alterations as, for example, infarction with hypo- or dyskinetic areas in the ventricular wall, or aneurysm. These cases are both the most frequent ones and the cases in which this combined technique has the most to contribute.

This non invasive procedure, which can be repeated as often as necessary, is an important contribution in the follow up of coronary artery diseases and also before and after surgery.

For a simple tracer dose, views at various angles and projections may be performed, which allows, in some cases, the detection of slight abnormalities in myocardial function. Our second case was an example of the value of combining the two studies: multigated technique applied to both myocardium and blood pool increases the precision of topographic and kinetic data, and provides qualitative determination of left ventricular functional parameters. Correlation with ventriculography was good. Outlines of the left ventricle from radiological and radioisotopic images were in good agreement for demonstrating wall motion disorders.

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Book review

Exercises in Diagnostic Radiology—8 Diagnostic Ultrasound. By B. B. Gosink and L. F. Squire, pp. 183, illus., colour, 1976 (W. B. Saunders Co., Philadelphia, London, Toronto), £6·00.

This volume in the "Exercises in Diagnostic Radiology" series, like its predecessors, aims to teach by illustrated examples. The main body of the text consists of a series of problems potentially soluble by ultrasound techniques, each with a capsule clinical summary and a single ultrasound tomogram. The reader is invited to reach a diagnosis before turning the page to read what became of the patient. The whole field of diagnostic ultrasonics is covered, including the abdomen, obstetrics, opthalmology, echo-encephalography and echo-cardiography.

An initial section on the elements of the physics of ultrasound is supplemented by more detail in each of the main following sections covering points relevant to the particular anatomical problems. The book is imaginatively assembled with excellent integration of the roles of ultrasound and conventional radiology as well as nuclear medicine. There are useful summaries at the end of each section on the sorts of problems to which ultrasound may be expected to contribute diagnostic information.

Inevitably, in a book of this size the subject is not covered in any great depth, and it is more useful as a short introduction to the subject for physicians or radiographers than as a manual for ultrasound specialists, but it will also be useful as quick revision material for those facing specialist exams.

The abdominal and obstetrics section suffers from a particular weakness in that too few ultrasound tomograms are presented in the question part of each diagnostic problem. Unlike conventional radiology or isotope imaging where a single picture may contain all the information obtained from a particular projection, ultrasound scanning is tomographic and a full impression of the area being scanned requires the mental integration of a number of the two-dimensional tomograms. Any single view is likely to be unrepresentative and certainly no diagnostician would contemplate making a diagnosis with only one view available. Thus the exercises presented are unrealistic and in principle are misleading. Apart from this the material is good and is well and accurately presented in a racy conversational style which some readers will find an aid to concentration and others merely an irritation.

D. O. Cosgrove.

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The determination of anatomical cross-sections using a radiotherapy simulator

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ABSTRACT

A system for obtaining anatomical cross-sections for treatment planning using a radiotherapy simulator is described. A fluorescent screen is viewed by a low light level Isocon television camera and the video signal is digitized and stored. Many projections of the phantom are obtained by rotating the simulator gantry. A convolution algorithm has been used to reconstruct chest sections in which skin and lung outlines are visible. The technique could also be used to make corrections to radiotherapy dose distributions where irradiation of lung tissue is involved.

Accurate radiotherapy treatment planning requires a knowledge of cross-sectional anatomy, for three main reasons. First, the physical extent of the tumour and its relation to surrounding tissues must be known in order to select the correct size and orientation of the X-ray fields. Second, critical organs may need to be shielded and this can only be done if their position is known. Third, an estimate of the cross-sectional density distribution enables a correction to be made for the attenuation of the X-ray beam in differing materials and the subsequent modification of absorbed dose distributions. The skin outline can also be derived from the cross-sectional image.

The development of computed tomography has provided this knowledge, although such systems are expensive and often remote from other treatment planning apparatus. There are clearly advantages in using existing treatment planning equipment, *e.g.* radiotherapy simulators, for the production of cross-sections (Harrison and Farmer, 1976). Photographic film in conjunction with a simulator (Webb *et al.*, 1977) and video signals from X-ray fluoroscopy systems (Kak *et al.*, 1977; Lantz *et al.*, 1975) have also been used to produce cross-sections. This paper describes some preliminary results in the derivation of anatomical cross-sections using a radiotherapy simulator with a television viewing system and the methods of computed tomography.

SUMMARY OF THE THEORY OF COMPUTED TOMOGRAPHY

Consider a section of a phantom irradiated by many independent pencil beams of X rays (Fig. 1). If the section can be represented by a two-dimensional distribution of attenuation coefficient $\mu\ (x,y)$ then

$$I_\theta(x') = I_0 \exp\left[-\int_{-\infty}^{\infty} \mu\,(x,y)\,\mathrm{d}y'\right] \quad . \quad (1)$$

where I_0 is the initial beam intensity and $I_\theta\ (x')$ is the transmitted intensity when the beam has been rotated through an angle θ to the x axis.

Using equation (1) we define a projection of the section at an angle θ as

$$\mathrm{P}_\theta(x') = \ell n\, \frac{I_0}{I_\theta}\,(x')$$

$$= \int_{-\infty}^{\infty} \mu\,(x,y)\,dy' \quad . \quad . \quad . \quad (2)$$

We wish to estimate $\mu\ (x,\ y)$ from a number of projections at various angles θ. This problem has received considerable attention in recent years and has been reviewed by Brooks and DiChiro (1975) and Pullan (1976).

The method chosen in this study is the convolution or filtered back-projection technique. The concept of back projection is illustrated in Fig. 2. The value of $\mu\ (x,\ y)$ at a point Q in a section is proportional to the sum of the corresponding projection values at x_1', x_2', x_3' etc. It can be shown (Gilbert, 1972) that a section reconstructed using this simple scheme results in a picture which is "blurred" by convolution of the "true" picture with a $1/r$ function where r is the radial distance from the origin of this function. This blurring can be removed by filtering the Fourier transform of each projection with a function $F\,(X)$ shown in Fig. 3A followed by performing the inverse Fourier transform. Thus if $G_\theta\,(x')$ is the modified projection then

$$G_\theta(x') = \mathcal{J}^{-1}\{\mathcal{J}\{\mathrm{P}_\theta(x')\}\,.\,F(X)\} \quad . \quad (3)$$

where $\mathcal{J}$ denotes the Fourier transform and $\mathcal{J}^{-1}$ the inverse Fourier transform.

Back projection of $G_\theta\,(x')$ results in a reconstruction in which the blurring has been removed. The high frequency cut-off in the filter $F\ (X)$ implies that no frequencies greater than $X_{\max}$ will be present

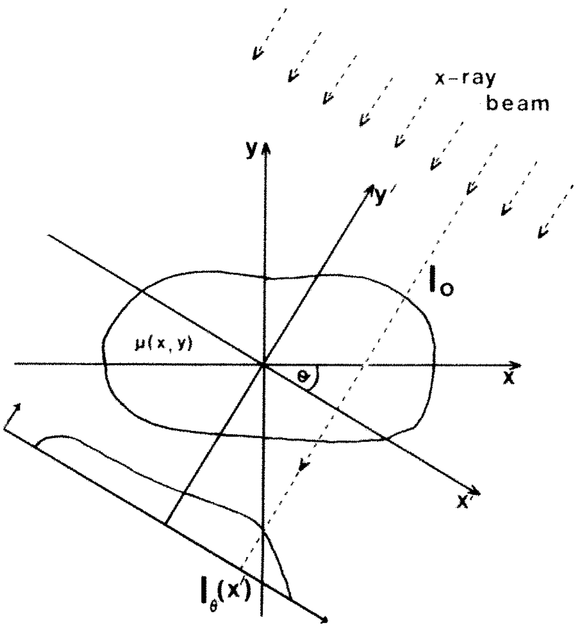
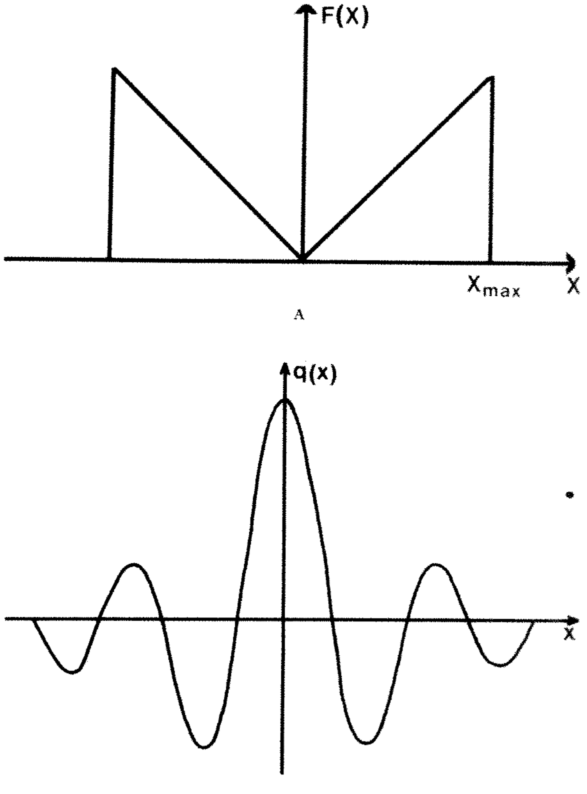


FIG. 1.
Projection of an object using a parallel beam of X rays.



A

B

FIG. 3.
(A) Ramp function $F(X)$ in frequency space.
(B) $q(x)$, Fourier transform of $F(X)$.

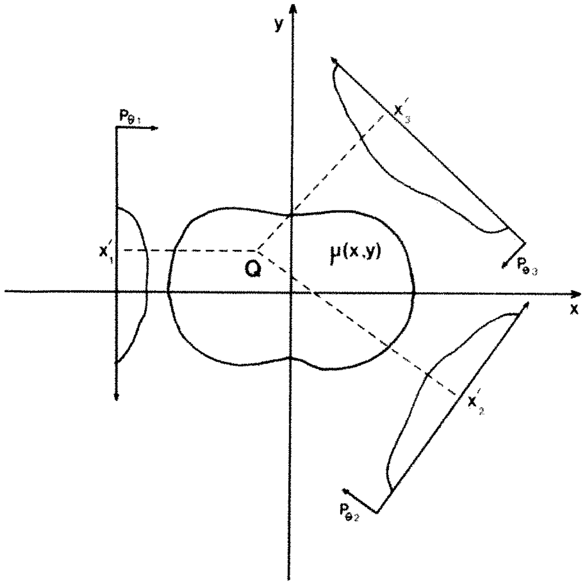


FIG. 2.
Back projection for three orientations of the X-ray beam.

in the reconstruction, thus setting a limit to the resolution attainable.

The modified projections $G_\theta\,(x')$ may also be obtained by performing a convolution operation in real space rather than a filtering operation in frequency space (Pullan, 1976).
Thus

$$G_\theta\,(x') = P_\theta\,(x') * q\,(x') \quad . \quad . \quad . \quad (4)$$

where * denotes the convolution operation and

$$q\,(x') = \mathcal{F}^{-1}\,\{F\,(X)\} \quad . \quad . \quad . \quad . \quad (5)$$

$q\,(x')$ is shown in Fig. 3B. Evaluation of $q\,(x')$ and further discussion is given by Gilbert (1972), Bracewell and Riddle (1967) and Ramachandran and Lakshminarayanan (1971).

Some modification of the basic function shown in Fig. 3A is possible in order to achieve smoothing and to reduce the oscillatory nature of $q\,(x)$ caused by the abrupt cut-off of $F\,(X)$ at $X_{\max}$ (Chesler and Riederer, 1975). The number of projections N needed for uniform resolution has been given by several authors (*e.g.* Bracewell and Riddle (1967)) as:

$$N \geqslant \pi M X_{\max} \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where M is the maximum spatial extent of the object. This theory assumes narrow parallel beam conditions. Practical departures from this theory will be discussed in a later section.

EXPERIMENTAL MEASUREMENT OF PROJECTIONS USING A RADIOTHERAPY SIMULATOR

Description of simulator

The machine used in this study is an extensively modified T.E.M. Ximatron with a novel viewing system (Farmer and Ross, 1975; Thompson, 1977). A 48.5 × 48.5 cm fluorescent screen is viewed by a low-light level Intensifier Isocon television camera P 8096 (English Electric Valve Co. Ltd.) This instrument consists of a single stage 40 mm Image Intensifier optically coupled to a 55 mm Image Isocon (P 8041). The large screen enables entire chests, for example, to be viewed without recourse to the "scanning" procedure often employed in commercial machines.

For computed tomography applications the X-ray beam is collimated to form a narrow fan of dimensions 48.5 × 2.0 cm at the screen (Fig. 4). The scattered radiation intensity at the screen is reduced by use of a crossed grid and the unused portions of the screen are optically masked to eliminate light produced by leakage of primary radiation. The screen is viewed by the television camera via an angled mirror so that the TV lines are parallel to the long axis of the illuminated strip. A single TV line passing through the centre of the strip consists of a voltage which is modulated by some function of the transmitted X-ray intensity and therefore represents a projection. If the TV line is digitized and stored, several projections can be accumulated by rotating the gantry. Figure 5 shows the external appearance of the simulator with the X-ray head on the right and the viewing system on the left of the picture. Both units are attached to the rotating gantry.

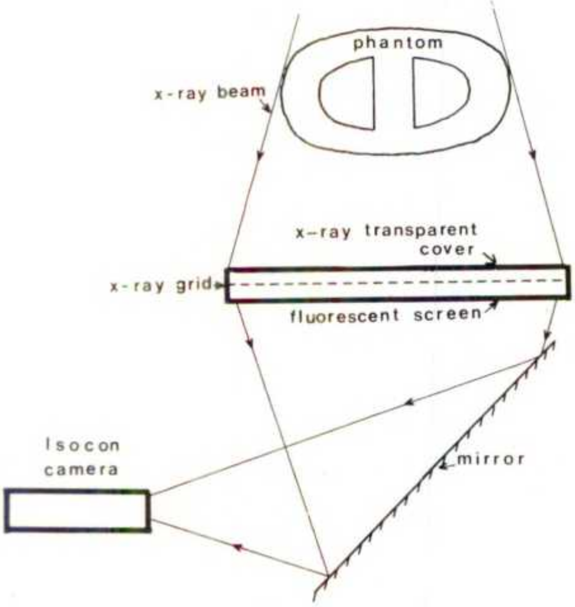


FIG. 4.
Schematic diagram of the simulator viewing system.

Video line sampling and storage

Figure 6 shows a schematic diagram of the sampling operation. Upon receipt of an external trigger, at a particular gantry angle, the video signal is sampled at 2.6 MHz by a Serial Analogue Memory device (Reticon Corp) which stores, in analogue form, 128 samples of the signal.

When the read-in cycle is complete a pulse is supplied to a DEC PDP-8 I computer which initiates the read-out cycle. The 128 samples are transferred sequentially to the computer at 11 kHz for analogue to digital conversion in 256 levels, and the data stored in core memory. The system is then ready for further collection of data. The complete set of data has, for experimental purposes, been transferred on paper tape to an IBM 370 computer at the University of Newcastle upon Tyne, as input to the convolution algorithm. This large computer system provides the facilities necessary for program development although an on-line system employing a mini-computer is likely to be a more practical solution in the hospital.

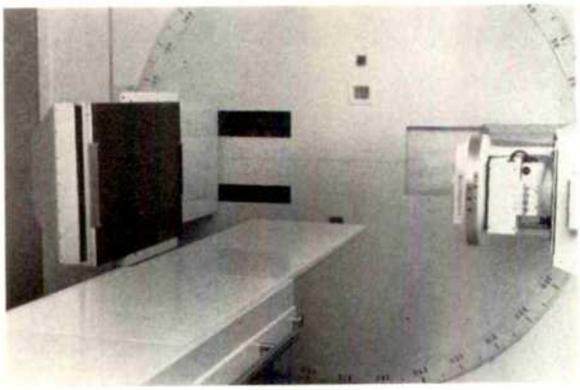


FIG. 5.
The radiotherapy simulator showing X-ray head (right) and viewing system (left) mounted on rotating gantry.

Diverging beam geometry

The theory given above assumes that a parallel X-ray beam is used. Several modifications to the theory for the case of fan beams have been suggested. The projection data from the diverging X-ray beam can be rearranged so that approximations to a parallel beam result (Wang and Cho, 1975) or multiple convolutions can be performed to allow for divergence (Pang and Genna, 1975).

It can also be shown that back projection of the projection data along converging trajectories followed by a two-dimensional frequency filtering operation (or two-dimensional spatial convolution) leads to the correct reconstruction (Budinger and Gullberg, 1975). For the relatively small angle of divergence used in this work (16 deg.), a simple correction has been made whereby the projection data are convoluted as described above and the resulting modified projections back-projected along converging ray paths which represent the geometry of the X-ray beam used.

Camera transfer characteristics

It is important to relate the magnitude of the video voltage to the luminance of the fluorescent screen. It is assumed that the luminance is directly proportional to the incident X-ray intensity. Deviations from this condition due to beam hardening effects (Baily and Keller, 1976) are under examination but have been ignored in this preliminary study. Experiments with an electroluminescent screen whose luminance can be controlled have enabled the transfer characteristics of the Isocon camera to be measured (Fig. 7). At the low light levels used, the relationship between video voltage (V) and X-ray intensity (I) is taken to be

$$V \propto I^m \qquad . \quad . \quad . \quad . \quad . \quad . \qquad (7)$$

where m is a constant.

At higher levels of luminance the "knee" of the transfer characteristic is encountered and m is no longer constant. It is desirable therefore to operate the camera in the region below the "knee". From equations (2) and (7) we have

$$P_\theta(x') = \frac{1}{m} \ln \frac{V_0}{V_\theta(x')} \qquad . \quad . \qquad (8)$$

Thus $P_\theta(x')$ is easily determined since V_0 and $V_\theta(x')$ are the video voltages corresponding to I_0 and $I_\theta(x')$ respectively. The importance of measuring the transfer characteristics of an individual TV camera system when quantitative measurements are to be made has been stressed by Baily and Keller (1976).

In practice, the unattenuated beam profile $V_0(x')$ and the beam profile with phantom $V_\theta(x')$ are measured and $P_\theta(x')$ calculated for each of 128 values of x'.

THE RELATIONSHIP BETWEEN SENSITIVITY AND SPATIAL RESOLUTION

An expression for the relationship between sensitivity, spatial resolution and radiation dose has been given by Pullan (1976). If we allow for the camera transfer characteristic (equation 7) then we may write for an element of the phantom of dimensions $a \times a$ and depth h:

$$D \propto \frac{v^2 S}{ah} \qquad . \quad . \quad . \quad . \qquad (9)$$

where D is the radiation dose

v is the sensitivity ($v = \mu / \delta\mu$) . .

$$S = \int_{-\infty}^{\infty} q^2(x)\, \mathrm{d}x \qquad . \quad . \qquad (10)$$

and $q(x)$ is the convolution function (Fig. 3(b)).

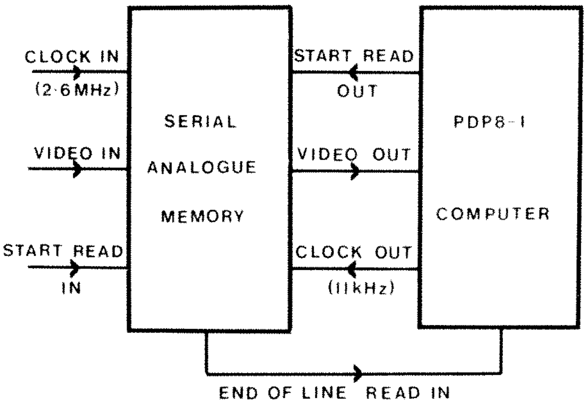


FIG. 6.
Block diagram showing the sampling and storage of a TV line.

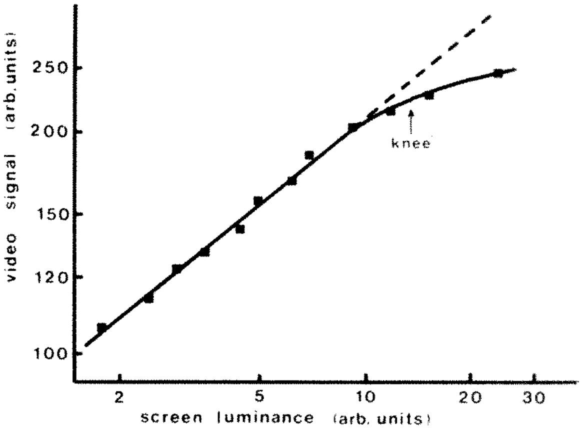
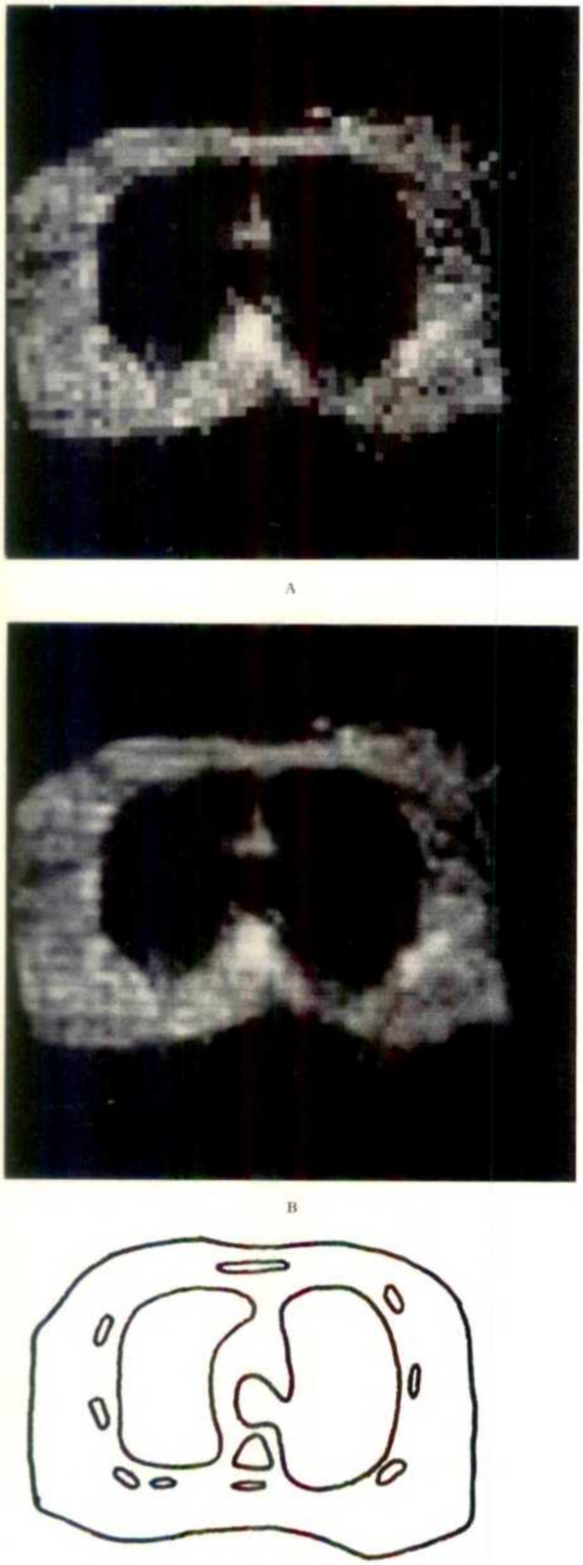


FIG. 7.
Transfer characteristics of the Isocon camera (log scales).



For a simple ramp function where the projection data $P_\theta(x')$ are sampled at intervals of a,

$$S \propto \frac{1}{a^2}$$

and equation (9) reduces to the form given by Pullan (1976) *i.e.*

$$D \propto \frac{v^2}{a^3 h}$$

If a^{-1} represents the resolution of a reconstruction and v^{-1} represents the inaccuracy in the value of a picture element then

$$\left(\frac{1}{a}\right)^3 \propto \left(\frac{1}{v}\right)^2 \quad c.f. \text{ Hounsfield (1976)}$$

Thus for a given dose, an increase in sensitivity can be achieved at the expense of spatial resolution. Conversely, an increase in the resolution (decrease in a) means that the sensitivity is reduced and the projection data must be sampled at finer intervals.

For the system described here, the projection data are sampled at 128 points per projection and the reconstruction mapped onto a 64 × 64 matrix. An increase in sensitivity without further degradation in resolution implies that h and D need to be increased. In practice this means that several adjacent TV lines should be averaged and that the X-ray tube current should be increased. An increase in dose is not necessarily disadvantageous when the technique is used in radiotherapy treatment planning, since the dose will in any case be much smaller than the subsequent therapy dose.

RESULTS

Sixty projections of a chest phantom at 4 deg. intervals were taken using a 100 kV X-ray beam filtered by 1.5 mm Al and a tube current of 3 mA. Fig. 8A shows a reconstruction made under these conditions and displayed on a 64 × 64 matrix. The skin and lung outlines can clearly be seen and the spine is discernible.

Figure 8C is a tracing of the actual phantom made as close as possible to the position of the

FIG. 8.

Reconstructions of a chest phantom.

(A) 60 projections, 4 deg. increments, 64 × 64 matrix.

(B) 60 projections, 4 deg. increments, 256 × 256 matrix, by interpolation using same basic data as (A).

(C) Outline of the section irradiated. Note the unfortunate lack of realism in the present phantom.

irradiated section and scaled appropriately. Figure 8B is the same reconstruction as Fig. 8A but displayed on a 256×256 matrix, using linear interpolation (Fenwick, 1977). The correction for diverging beam geometry described above was used and the convolution method applied using the discrete form of the convolution function (Ramachandran and Lakshminarayanan, 1971) with no smoothing.

The phantom consisted of a skeleton embedded in uniform tissue-equivalent rubber with uniform lung-equivalent sponge. It is difficult to predict the detail that would be seen in a real chest section, but it would appear that the contrast between lung and tissue would permit the visualization of a tumour of moderate size invading the lung.

Conclusions

Preliminary experiments have shown that a radiotherapy simulator of the design described can be used to produce anatomical cross-sections of the body. The quality of the picture obtained so far compares unfavourably with that of modern CT scanners and this is attributable to a number of factors.

First, owing to the sampling method used, the efficiency of photon utilization is poor, resulting in random noise in the image.

Second, the picture quality is limited by the relatively small number of projections (60) we have used; an increase in this number as well as in the tube current (and hence patient dose) would improve both sensitivity and resolution.

Third, electronic noise in the camera is a possible cause of picture degradation at the very low light levels present. Accurate adjustment of the camera is essential and work is still in progress on the optimum camera characteristics for operation at low levels of light.

Despite these limitations the reconstruction shown in Fig. 8 shows detail which may be sufficient to be of value in radiotherapy planning, where the purpose of cross-sectional imaging is to reproduce essential anatomical detail and not necessarily to be of very high diagnostic value.

It is felt, therefore, that the combination of a simulator with such a computed tomographic facility has considerable potential and already shows some value in radiotherapy, making use as it does of the existing engineering and X-ray facilities of the simulator and adding only a relatively small amount to the total cost both of equipment and accommodation in the hospital.

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Thyroid uptake measurements: the influence of gland depth, gland mass and lobe separation

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ABSTRACT

Phantom measurements were carried out to define the dependence of standard thyroid uptake measurements on gland depth, gland mass and lobe separation. In the case of ^{99}Tc^{m} and ^{131}I, depth can cause a variation of up to a factor of two in the apparent uptake, while in the case of ^{125}I the variation due to depth is a factor of about four. By contrast, gland mass and lobe separation cause only small errors, of the order of 2 and 10% respectively for medium energy isotopes. These errors are particularly important when the uptake value is used to guide prescription of ^{131}I for therapy of thyrotoxicosis.

Quantitative measurement of the amount of radioactivity in the thyroid after administration of tracer doses is the object of tests usually referred to as uptake measurements. The techniques widely used at present for this type of test involve comparison of the count rate over the surface of the neck, anterior to the thyroid, with the count rate over a neck phantom containing a model thyroid under specified conditions of geometry (Goolden, 1971). Thus the neck phantom acts as a true standard for the amount of activity administered to the subject only to the extent that the phantom and model thyroid conform to the geometrical and attenuation conditions present in the patient (Schulz and Rollo, 1970; Sear, 1970). These conditions can be specified by reference to the depth of the gland, its mass, and the separation of its lobes. While it is known that these factors can influence the accuracy of an uptake measurement, corrections are not generally applied for them, with the possible exception of situations in which ^{125}I is used (Rhodes and Wagner, 1971). The only corrections to conventional uptake measurements applied with any degree of regularity are those concerned with extra-thyroidal activity (Goolden, 1971).

Lack of attention to the role of geometry and attenuation may arise from a serious underestimation of their importance. As illustrated below, in the case of the 24 hour uptake these variables may be responsible for uptake estimates whose values differ by more than 100%, which is much larger than any error that might be contributed by extra-thyroidal activity. It is also likely that the decline of the uptake measurement as a diagnostic investigation, following the introduction of reliable laboratory indices of thyroid function, has reduced the incentive to resolve difficulties associated with its accuracy (De Groot and Stanbury, 1975). Nevertheless uptake measurements are still used in one situation where accuracy is of paramount importance, that is as a guide to dose prescription in radioiodine therapy. Recent indications in this field suggest that radiation dose may be more closely related to clinical prognosis than was previously thought to be the case (Malone and Cullen, 1976). Therefore the importance of accurately evaluating dose, and hence radioiodine uptake, is if anything increased in this area. In this paper the influence of gland depth, mass and lobe separation on the outcome of uptake measurements is studied *in vitro* using a phantom. Three isotopes (^{131}I, ^{99}Tc^{m}, and ^{125}I) which are frequently involved in thyroid investigations were used.

MATERIALS AND METHODS

Counting procedures

For measuring uptake a probe in which the detecting element was a 5 cm × 5 cm NaI (Tl) crystal was used. This was housed in a 6 cm diameter parallel-sided lead collimator, the leading edge of the crystal being recessed 10 cm into the shielding. As this is not a standard IAEA collimator, point spread functions were determined for each isotope to ensure that the largest thyroid models would be completely within its field of view at the working distances used (Goolden, 1971). The field of view was defined to include the area in which the point spread function was greater than 90% of its maximum value. Under these conditions working distances of 30 cm for ^{131}I and ^{99}Tc^{m} and of 40 cm for ^{125}I were found to be satisfactory.

The entire photopeak of the main emission(s) from each isotope was included in the counts recorded. This corresponded to energy windows of 328–400 keV for ^{131}I, 119–161 keV for ^{99}Tc^{m}, and 20–39 keV for ^{125}I. The activities used for measurements varied but were generally of the order of 50 μCi. These activities were insufficient to saturate the counter. At least 50000 counts were recorded in each observation.

TABLE I

Relative counts from model thyroid 3 cm deep in water or tissue equivalent medium

Medium	Relative counts (%)		
	^{131}I	^{99}Tc^{m}	^{125}I
Tissue and bone equivalent	100 ± 1.6	100 ± 2.1	100 ± 2.9
Water	101.1 ± 1.6	103.2 ± 2.1	112.3 ± 2.9

TABLE II

Dimensions of lobes of model thyroids

"Thyroid" Mass, (g)	"Lobe" dimensions, (cm)	
	Height	Diameter
10.0	3.03	1.45
15.0	3.73	1.60
30.0	4.77	2.00
40.0	5.51	2.15
60.0	5.65	2.60

Thyroid and neck phantoms

The neck phantom consisted of a 14 cm diameter by 16 cm high Perspex cylinder of wall thickness 5 mm. The phantom was filled with water during measurements with ^{131}I and ^{99}Tc^{m}. When ^{125}I was being used a tissue equivalent medium and a model spine (5 cm diameter) made of bone equivalent material was necessary instead of water (Table I). The composition of the tissue and bone equivalent media will be fully reported elsewhere (O'Connor, *et al.*, 1978). Small plastic bottles of various dimensions were used to simulate the lobes of thyroid glands whose masses would lie in the range 10–60 g (Table II). The lobes were suspended on a polystyrene mount which allowed their separation and depth to be adjusted.

Presentation and treatment of data

Gland size was specified in grams and was equal to twice the lobe mass. No account was taken of the isthmus. Lobe separation was defined as the distance between the centre points of each simulated lobe, and the maximum value used was 6.5 cm. Gland depth was normally specified as the perpendicular distance from the midline of the anterior surface of the neck phantom to the centre of gravity of the thyroid system, *i.e.* the mid-point of the line joining the centres of the two lobes. The maximum depth used was 6.5 cm. In one instance (Fig. 3, broken line) gland depth was specified as the distance between the anterior surface of a lobe and the point on the neck phantom immediately anterior to it.

To simplify data presentation one particular configuration of thyroid mass and geometry had to be selected as the standard to which other measurements could be referred. The standard chosen was a 30 g thyroid at a depth of 3.0 cm with lobe separation of 3.5 cm, which is fairly typical of the situation in the population whose uptake is measured. The results were expressed as the correction factor by which a measured "uptake" must be multiplied to convert it to the true value, assuming a standard with the above properties was used.

To render the charts legible smooth curves were fitted to the data points using a quadratic of the form

$$y = a_0 + a_1x + a_2x^2$$

Nine points were used for each curve in Fig. 1. In Fig. 2, four points were used for each curve in the left panel and twenty points for each composite line in the right panel. In Fig. 3, the data points are included with the curves.

Results

In Fig. 1 the effect of gland depth on uptake measurements is presented for three gland masses, using ^{131}I, ^{99}Tc^{m}, and ^{125}I. The ordinate in all cases is the correction factor by which the measured uptake must be multiplied to convert it to its true value, assuming the standard of activity used was a 30 g model thyroid with lobe separation 3.5 cm and depth 3.0 cm. The correction factors required for ^{131}I and ^{99}Tc^{m} are remarkably similar, ranging from 0.8 for very superficial glands (2 cm deep) to 1.6 for deep glands (6 cm deep). With ^{125}I the effect of depth is much more pronounced, as might be expected, with the correction factor going from 0.7 to 3.0. Thus an apparent uptake measurement may vary over a factor of two with ^{131}I or ^{99}Tc^{m}, and a factor of four with ^{125}I, due to variation in the depth of the gland alone.

Surprisingly, Fig. 1 suggests that the effect of gland mass and lobe separation on apparent uptake is relatively small. Figure 2 presents, on an expanded scale, the influence of lobe separation alone. A separation of 3.5 cm was taken as standard. The left hand panel shows that the correction factor for ^{131}I varies from 0.96 to 1.02, being less than unity for well separated lobes. Each configuration of gland mass and depth has a slightly different line representing the correction factor for lobe separation. However, with the exception of very large superficial glands (60 g, 2.5 cm depth) these lines lie sufficiently closely together, and the corrections involved are sufficiently small, for the mean value of

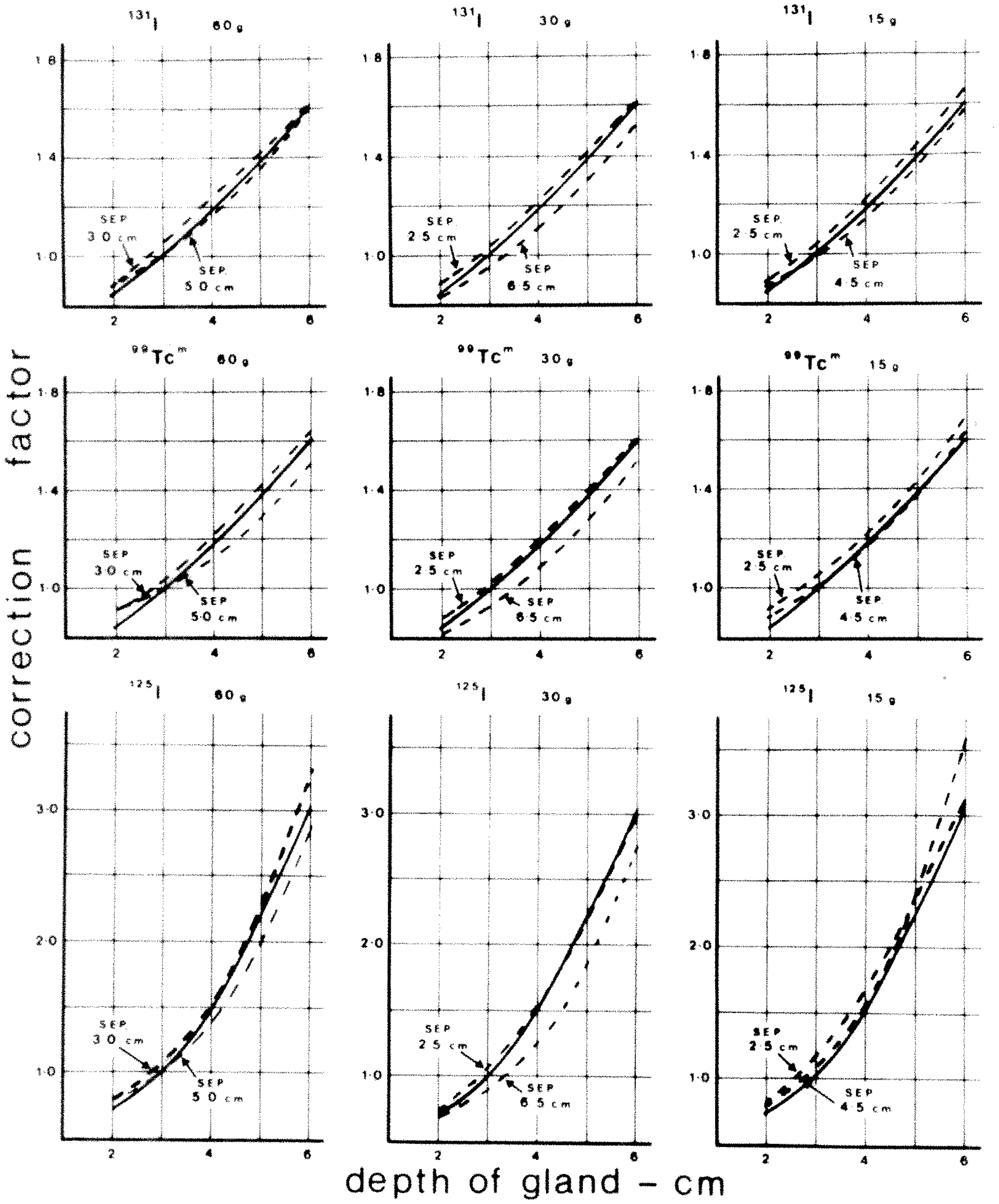

FIG. 1.

The correction factor by which the apparent activity of ^{131}I (top), ^{99}Tc^{m} (centre), and ^{125}I (bottom) must be multiplied to give the true value. Values are plotted as a function of depth. The heavy line in each panel is for a standard 30 g gland with 3.5 cm lobe separation. The broken lines correspond to glands whose masses are given at the top of the panel (15, 30 or 60 g), with lobe separations indicated beside the line.

the separation correction factor over the range of depths and gland masses to be used in practice. The right hand panel in Fig. 2 presents the mean lobe-separation correction factors for the three radionuclides used. Those for ^{131}I and ^{99}Tc^{m} are relatively similar ranging from 0.96 to 1.02. With ^{125}I the factor goes from 0.86 to 1.06 and is consequently more significant. These are mean values and may be used without the introduction of large errors. However, if absolute values of the uptake are required to

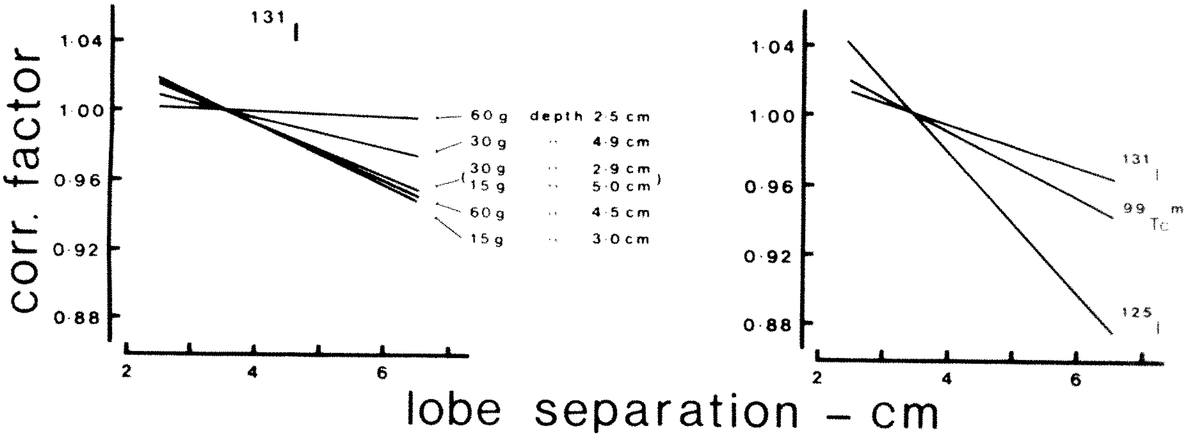

FIG. 2.

Correction factor by which apparent activity in model thyroids must be multiplied to compensate for lobe separation.

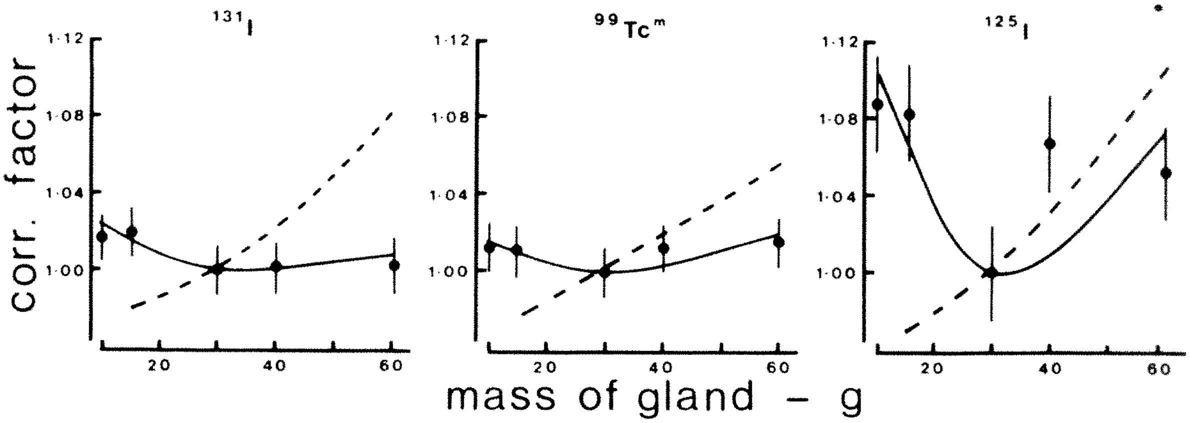

FIG. 3.

Correction factor by which apparent activity in model thyroids must be multiplied to compensate for gland mass using standard co-ordinate system (full lines) and a co-ordinate system in which depth is specified to the anterior surface of the thyroid lobes (broken lines). The data points refer to the full lines only.

within 2% the influence of lobe separation must be determined *de novo* for each new configuration encountered.

The full lines in Fig. 3 present the correction factor as a function of gland mass for constant depth and lobe separation using a 30 g gland as standard. The full lines are based on a quadratic fit to the data points presented. The factors are all greater than unity but represent very small absolute corrections. For ^{131}I and ^{99}Tc^{m} the maximum value is less than 1.015, representing a departure of less than 1.5% from the true value. With ^{125}I the maximum value is 1.1, seen for very small glands. These data are based on mean values of the correction factor for gland mass and hence are subject to the same limitations as those in Fig. 2.

It should be noted that the specification of depth used in all of the above measurements is the perpendicular distance from the anterior midline of the neck phantom to the centre of gravity of the thyroid system. If an alternative depth specification is introduced, for example the distance between the anterior point on a lobe and the corresponding point on the neck phantom in front of it, the results in the full lines of Fig. 3 will be altered as they are based on an assumption of constant gland depth. The broken lines in Fig. 3 present the variation in the correction factor with mass using the alternative co-ordinate system. In this case the range of variation in the correction factor is larger, because the depth of the centre of activity in each lobe recedes further into the neck phantom as the gland mass increases.

In Table III the effect of distance and attenuation separately on the count rate from a point source

TABLE III

Effect of distance and attenuation separately when the depth of a point source changes from 3 cm to 6 cm

Depth (cm)	Relative counts (%)		
	Radionuclide (medium)		
	^{131}I (air)	^{99}Tc^{m} (air)	^{125}I (air)
Distance alone			
3 cm	100	100	100
6 cm	84.7 ± 1.2	84.1 ± 0.9	87.7 ± 1.8
	^{131}I (water)	^{99}Tc^{m} (water)	^{125}I (water)
Attenuation alone			
3 cm	100	100	100
6 cm	79.8 ± 2.0	79.4 ± 2.2	40.6 ± 3.4

placed 3 cm and 6 cm deep in the neck phantom are recorded. The effect of distance alone on the count rate from ^{125}I is smaller because of the larger working distance of the detector from the neck phantom. However, in all cases attenuation is the larger effect and is remarkably similar with ^{131}I and ^{99}Tc^{m}.

From the data presented above it is possible to determine the true thyroid uptake (*U*) provided the depth, lobe separation and mass of the gland are estimated. The true value will be given by

$$U = U_m \, C_d \, C_s \, C_m$$

where C_d, C_s and C_m are the correction factors for depth, lobe separation and mass read from Figs. 1, 2 and 3. U_m is the measured uptake, assuming the standard used corresponds to a 30 g gland, 3.0 cm deep, with a lobe separation of 3.5 cm.

Discussion

The results presented demonstrate a strong dependence of the apparent activity in a simulated thyroid on its depth in a neck phantom, and a weaker dependence on lobe separation and gland mass. The necessity to correct uptake values for depth is well known for ^{125}I (Rhodes and Wagner, 1971) and although not widely practised for ^{131}I has previously been studied and discussed (Vennart, 1962; Schulz and Rollo, 1970; Sear, 1970). The main contributions to the correction factor as depth increases are distance and attenuation. As illustrated in Table III, attenuation is the most important of these, though neither can be neglected. A surprising feature of the present results is the almost identical behaviour of ^{99}Tc^{m} and ^{131}I, which might not have been expected in a situation where attenuation is important. However, inspection of mass energy absorption coefficients for the main emissions of these isotopes reveals that they are both within 10% of 0.03 cm^2/g, thereby accounting for the similarity in their behaviour (N.B.S., 1964). The much greater effect of depth on ^{125}I may be explained by the larger coefficient of about 0.1 cm^2/g for the photons detected from it.

The increase in apparent uptake with larger lobe separation (Fig. 2) results from a complex interplay of geometrical and attenuation factors. The most likely explanation lies with the cylindrical surface of the neck phantom, which will cause a reduction in the amount of absorber that lies between the thyroid and the detector as lobe separation increases. It should be noted, however, that not all patients have cylindrical necks, and that with obese patients the anterior neck surface may be relatively flat. In such cases a correction for lobe separation may not be appropriate. The compensation required for gland mass is relatively small. Presumably this is a result of the fact that equal amounts of activity will be distributed in front of and behind any selected depth in the neck regardless of mass, provided the depth co-ordinates are referred to the centre of gravity of the thyroid system. If the co-ordinates are referred to the anterior of the thyroid lobes, the centre of activity in the neck becomes deeper as gland mass increases, and hence a larger correction factor (Fig. 3) is required.

The data presented above indicate how seriously misleading a thyroid uptake measurement may be. The errors for ^{131}I and ^{99}Tc^{m} are about half those for ^{125}I. Thus, even with these higher energy nuclides, it is possible that a thyroid whose true uptake is 40% may give readings anywhere between 27 and 57%. The incidence and extent of such errors are obviously dependent on the distribution of thyroid depth in the population referred for uptake studies. The data available on thyroid depth are not extensive, but consistently have a mean value between 3 and 4 cm. Furthermore such studies as exist have shown the distribution of depths to be broad, with a standard deviation between 1.6 and 2.0 cm (Schulz and Rollo, 1970; Vennart, 1962; Wellman *et al.*, 1967). Thus, a large proportion of the population will have thyroid depths that depart significantly from the mean value. For example Schulz and Rollo (1970) found that over 20% of patients had a thyroid depth greater than 4.75 cm. Experience with radionuclide scanning also indicates that lobe separation may vary broadly. Therefore there is a practical need to apply corrections for gland depth and lobe separation, if accurate values of the thyroid uptake are to be determined.

In diagnostic investigations of the thyroid relatively large errors in uptake may be regarded as tolerable owing to the existence of reliable and easily available laboratory investigations (De Groot and Stanbury, 1975). Nevertheless, it is not desirable, in the long term, to persist in quoting uptake values without taking some account of the influence of the factors studied above. Moreover it is likely that the variation in apparent uptake with depth contributes significantly to the wide normal range of uptake encountered in practice.

Wide margins of error may be acceptable in diagnostic applications of the uptake measurement. The same standards should not be applied in situations where the uptake is used to guide prescription of radioiodine dosage during therapy of thyrotoxicosis. Dose specification in this field has never reached the level of precision involved in conventional radiotherapy. Nevertheless recent work indicates that significant improvements are now technically possible (Rasmussen and Hjorth, 1974; Malone *et al.*, 1976; Cullen *et al.*, 1976), and that accurate dose specification may have some value in predicting the outcome of therapy (Malone and Cullen, 1976, 1977). Reliable uptake measurements are an absolute prerequisite for an accurate dosimetry system.

To improve the determination of uptake in practice using existing instruments it will be necessary to estimate gland depth and lobe separation. The latter can easily be achieved on a radionuclide scan. Several methods of measuring gland depth have been evaluated. These include methods based on the ratio of counts at two distances (Schulz and Rollo, 1970); the ratio of counts in the main peak to counts in a selected portion of the Compton spectrum (Rhodes and Wagner, 1971; Eversden *et al.*, 1968; Koral and Johnston, 1977); the ratio of thermoluminescent disc readings at the front and back of neck (O'Connor *et al.*, 1978); and perhaps use of a lateral scan. In the co-ordinate system described here the influence of gland mass has been minimized to such an extent that even the large uncertainty associated with clinical estimates of mass by palpation will not introduce significant errors into the uptake measurement (Smith and Wilson, 1967). Possible alternative approaches to accurate estimation of uptake are based on use of multiple probe systems (Sear, 1970; Plato and Jacobson, 1976) and on improvements in collimator design. Recently developed collimators, used in conjunction with a large crystal, yield a large volume in which response is relatively independent of organ mass or geometry, and hence may be suitable for application to the thyroid (Clarke *et al.*, 1977).

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Technical note

Tissue–air ratios for whole body irradiation with cobalt 60 gamma rays

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Total body irradiation with ^{60}Co γ rays has been used since about 1966 for the treatment of acute leukaemia (Johnson, 1968; Buckner *et al.*, 1970; Thomas *et al.*, 1971; Miller *et al.*, 1976). The method of irradiation developed by the Seattle group (Thomas *et al.*, 1975) requires knowledge of the dose at the mid-line of the body for calculation of the treatment time. Published data of tissue-air ratios (TAR) for elongated fields like the dimensions of a human body in the lying position are not available. It is only known from measurements carried out by Faw and Glenn (1972) that the TAR values along the central axis of the beam for square fields greater than 50×50 cm^2 show an effect of saturation. The objective of our investigations was to find TAR values for the mid-line of a human body.

EXPERIMENTAL

An Alderson phantom with a length of 150 cm, a mean lateral diameter of 30 cm and a mean A.P. diameter of 21 cm was used. The irradiation was carried out in a lateral direction with a field size of 165×30 cm^2, the centre of the beam being coincident with the diameter below the umbilicus. The source–mid-line distance was 4 m, which gives a decrease in air-dose of less than 4% at the ends of the phantom. The Alderson phantom was supported at a height of 1 m above the floor by a table consisting of a 2 cm wooden board and, beyond the field, a steel construction. The dose distributions were determined with small condenser chambers of diameter 0.6 cm and height 2 cm.* The resulting TAR values along the lateral body diameters below the umbilicus, across the middle of the pelvis and the lungs are presented in Table 1. One can see that the TARs in the abdomen and in the pelvis agree very closely, while the lungs have higher TARs.

The phantom was next reduced to a torso and then, step by step, further reduced in such a manner that the relative portions of pelvis, lungs and abdomen sections remained nearly the same. The distribution of TAR along the lateral diameter in the middle of the "mutilated" Alderson showed no measurable change down to a phantom length of about 60 cm.

The TAR values for an A.P. irradiation of the full phantom with a field size of 165×50 cm^2 are listed in Table II.

RESULTS AND CONCLUSIONS

For the Alderson phantom used, calculation of the equivalent square field from the well known formula of Worthley (1966) gives for a lateral irradiation direction a square of side S of 37 cm, for an A.P. irradiation a side S of 50 cm. The TAR values obtained for these equivalent fields are much too large with respect to the measured ones (Tables I and II). This is to be expected, since Worthley's formula firstly does not consider a saturation dimension and secondly is only valid for cuboids while the scattering volume of an elliptically cylindrical body whose cross-section is inscribed in the rectangular cross-section of the cuboid is of course smaller. If one applies Worthley's formula to the saturation length one gets equivalent fields of 31×31 cm^2 for the lateral irradiation and 40×40 cm^2 for the A.P. irradiation. The TARs are still too large, as shown in column 7 of Table I and column 5 of Table II. In order to overcome the remaining discrepancy we have supposed that, for a cylindrical body with infinite length, the contribution of scattered radiation to the TAR in the neighbourhood of the mid-line is proportional to the ratio of the cross-sectional area Q of the phantom to its circumference U. The same ratio applied to a square field of side S on a plane phantom surface would give a scatter contribution proportional to $S^2/4S$. We have therefore calculated the side S of an equivalent square by equating

$$\frac{Q}{U} = \frac{S^2}{4S} \qquad (1)$$

For finite but at least saturation lengths this relation is of course valid only along a central part of the mid-line. To test the validity of formula (1) we have investigated two phantoms with different shapes of cross section:

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*Manufacturer: Dr. Pychlau, Freiburg/Breisgau, Germany.

(1) a water phantom with plane A.P. surfaces, curved lateral surfaces, radius of curvature 10 cm, lateral diameter 20 cm, A.P. diameter 12 cm, length 50 cm;

(2) a water phantom with a cross-section of a circular segment of a "lateral diameter" of 16.6 cm, "A.P. diameter" 8.4 cm, length 50 cm.

In both cases the agreement between the experimentally obtained TAR values and those obtained using formula (1) for the equivalent square fields was within 2% in the vicinity of the central point of the mid-line.

For the practical application of formula (1) to human shapes the cross-section of an Alderson phantom or a patient can be approximated by an ellipse. With the mean lateral diameter d_1 as the large axis and the mean A.P. diameter d_2 as the small axis the cross sectional area becomes

$$Q=\frac{\pi d_1 d_2}{4} \quad . \quad . \quad . \quad . \tag{2}$$

Equation (1) can now be rewritten as

$$\frac{\pi d_1 d_2}{4U}=\frac{S^2}{4S} \quad . \quad . \tag{3}$$

Applying this to the Alderson phantom used for the measurements ($d_1=30$ cm, $d_2=21$ cm, $U=81$ cm) we obtain an equivalent square of 24×24 cm^2. Selected TAR values for this field are given in Tables I and II. For the lateral irradiation direction the TARs for this equivalent square are within 3% of the measured distribution in the abdomen and in the pelvis for lateral depths between 10 and 26 cm. We are not able to test the validity of formula (3) for the thorax because there are no published data on equivalent squares for lung tissue. For the A.P.

TABLE I

MEASURED ^{60}Co TAR VALUES IN AN ALDERSON PHANTOM AND CORRESPONDING VALUES FOR THREE SQUARE FIELDS (after Gupta and Cunningham (1966) and Faw and Glenn (1972)); irradiation direction: lateral (standard deviation ±2%)

Lateral depth (cm)	Alderson phantom			Square fields		
	Abdomen below umbilicus	Pelvis	Lungs	From equation (3) 24 × 24 cm^2	From Worthley's formula 37 × 37 cm^2	From Worthley's formula 31 × 31 cm^2
0	1.02	1.01	1.00	0.5 cm: 1.072	0.6 cm: 1.07	0.5 cm: 1.081
8	0.84	0.84	0.91	0.877	0.93	0.902
14	0.68	0.68	0.82	0.685	0.74	0.719
20	0.54	0.54	0.71	0.528	0.59*	0.564
28	0.345	0.365	0.55	0.362	0.42*	0.397
32		0.283	—			
32.5			0.450			

*Extrapolated

The depth 0 in Table I and II means that the dosemeter enclosed in a cap with sufficient wall thickness for electronic equilibrium was mounted on the surface of the phantom.

TABLE II

MEASURED ^{60}Co TAR VALUES IN AN ALDERSON PHANTOM AND CORRESPONDING VALUES FOR THREE SQUARE FIELDS (after Gupta and Cunningham (1966) and Faw and Glenn (1972)); irradiation direction: A.P. (standard deviation ±2%)

A.P. depth in cm	Alderson phantom	Square fields		
	Abdomen	From equation (3) 24 × 24 cm^2	From Worthley's formula 50 × 50 cm^2	From Worthley's formula 40 × 40 cm^2
0	1.03	0.5 cm: 1.072	0.6 cm: 1.07	0.6 cm: 1.07
6	0.90	0.940	1.00	0.98
12	0.75	0.744	0.84	0.81
18	0.58	0.576	0.69*	0.65*
22	0.51	0.482	0.60*	0.56*

*Extrapolated

irradiation direction we have only done measurements in the abdomen. The resulting TARs are within 3% of those of a 24×24 cm^2 field for A.P. depths between 8 and 20 cm. For a bilateral irradiation technique the above agreements extend to even larger ranges of depth.

ACKNOWLEDGMENTS

The authors thank Mr. A. Wolf and Mr. S. Faltermeier for their assistance in making the measurements.

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Book review

Progress in Nuclear Medicine, Vol. 4: Medical Cyclotrons in Nuclear Medicine. Edited by A. N. Serafini and J. E. Beaver, vi+202 p, illus., 1978 (S. Karger, Basel), DM 140.00.

This expensive little volume contains 25 of the papers presented at a meeting of medical-cyclotron users and others, at Miami Beach in March 1976. They are loosely grouped under the headings "Production aspects", "Chemistry overview" and "Clinical application of cyclotron produced products" (sic) and are in fact a very mixed bunch both in subject matter and quality of presentation.

The first section, for example, in addition to summaries of programmes and performance of 3 of the "dedicated" medical cyclotrons in the USA, also includes quite detailed descriptions of the special technology evolving at the Brookhaven and Los Alamos National Laboratories, where respectively 200 and 800 MeV proton beams, surplus to the needs of the nuclear physicists, are being used to make a limited number of radionuclides on a very large scale. In other papers, two more big and essentially physics-orientated machines, those at Indiana University and Vancouver, are discussed, and so is the stable isotope separation plant at Oak Ridge.

Included in the "Chemistry overview" section are papers on the preparation of water labelled with ^{14}O or ^{15}O, on ^{101}Rh^{m} production, and on the preparation and imaging with a positron-camera of ^{68}Ga radiopharmaceuticals. The remaining 6 papers each refer to a variety of radionuclides, with ^{123}I cropping up most frequently, and the preparation of the positron-emitters ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{62}Cu and ^{82}Sr also claiming a good deal of attention.

In the final section only one paper deals with a specific clinical application, the uses of $C^{15}O_2$ in cardiovascular disease, and this is essentially an extension of work carried out at Hammersmith in the early 60's. There is however, an interesting juxtaposition of papers concerned with two competing positron imaging systems; the MGH positron camera, and the UCLA version of PETT (positron emission transaxial tomography). This last paper also states a case for the development of a simple "baby" cyclotron, capable of generating the short-lived positron-emitting radionuclides which can now be imaged with such good resolution.

The meeting from which this volume stems was doubtless a stimulating one to its participants, but, unfortunately for the reader, the discussions—surely the most valuable part of such meetings—have gone unrecorded. Furthermore, it must be a matter of regret to the editors that the book contains no contributions from three of the most important and innovative medical cyclotron facilities in the USA, and only one from outside North America. In short, therefore, this book provides only patchy evidence of the value of dedicated medical cyclotrons, and cannot be regarded as a vital contribution to the literature of nuclear medicine.

D. J. SILVESTER.

1978, *British Journal of Radiology*, *51*, 463–466 JUNE 1978

Case reports

Left ventricular – right atrial communication with aneurysm of the membranous interventricular septum

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Defects in the atrial and ventricular septa are among the most common congenital heart lesions. An unusual form of ventricular septal defect, left ventricular-right atrial communication is a rare lesion which was first diagnosed preoperatively by Nordenström and Ovenfors (1960) and by Braunwald and Morrow (1960) by angiocardiography. We would like to report a case in which at angiography a left ventricular-right atrial communication was found in association with an aneurysm of the membranous portion of the interventricular septum, an association which has not been previously recorded.

CASE REPORT

The patient was a seven year old male with a heart murmur noted shortly after birth. Catheterization performed elsewhere during infancy was reported to show a ventricular septal defect. The patient was well during the interim. He was referred to Montefiore Hospital and Medical Center because of this history and for re-evaluation of his cardiac status.

On admission physical findings were limited to the chest, in an otherwise healthy boy. The cardiac apex was not displaced. A thrill was felt along the left sternal border and a grade IV/VI harsh holosystolic murmer was present. This was best heard at the left sternal border with radiation to the right of the sternum. The second heart sound was variably split. An intermittent third sound was heard at the apex. Electrocardiography revealed regular sinus rhythm with a axis of 0 degrees. An rSR′ pattern was noted in the right chest leads with a QRS of 0.1 second. The T waves and the QRS voltages were normal in the precordial leads. A chest radiograph showed mild cardiomegaly and a slight increase in pulmonary vascularity (Fig. 1). At catheterization both sides of the heart had normal pressures. Saturations revealed a step-up between the superior vena cava (average 74%), and the right atrium (average 82%). There were four paired samples with an average step-up of 7%. The average saturation in the pulmonary artery was 84% and the pulmonary/systemic flow ratio was 2:1. Exploration of the right atrium failed to reveal the presence of an atrial septal defect or anomalous pulmonary veins.

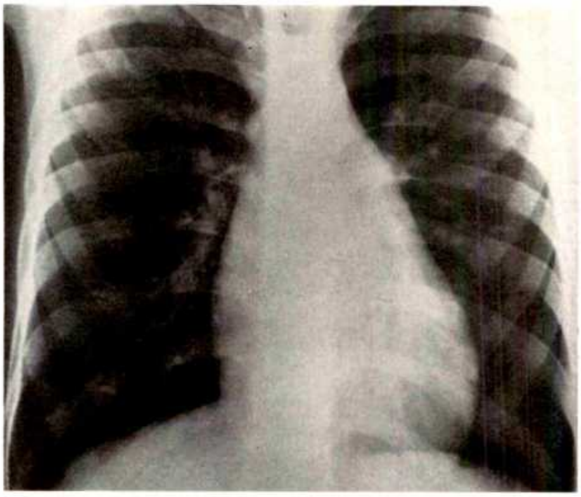


FIG. 1.

Mild cardiomegaly and overcirculation are revealed. The "ball-like" or globular configuration described in left ventricular-right atrial shunt is not observed here. Pulmonary/systemic flow ratio is 2:1.

Pulmonary angiography demonstrated overcirculation, and in the laevophase the left atrium was mildly enlarged. A distinct interatrial interface was observed. The left ventricle was normal. Opacification of the right atrium and then the right ventricle was noted directly thereafter. Retrograde left ventriculography clearly defined a left ventricular-right atrial shunt, with a jet of contrast entering the atrial lumen in systole (Fig. 2). In addition a large aneurysm of the membranous portion of the interventricular septum appearing separate and anatomically distinct from the shunt jet was delineated. The mitral valve was normal. Aortography revealed no prolapse of the aortic leaflets.

One month after catheterization the patient was readmitted for transatrial surgical correction. At surgery, the right ventricle and right atrium were the chambers predominantly enlarged. The pulmonary artery was dilated but not hypertensive. The atrial septum was intact. There was a communication between the left ventricle and the right atrium which was several millimeters in diameter, with tough fibrous margins. The defect was situated adjacent to the annulus of the tricuspid valve, in the area of the commissure between the septal and posterior leaflets of the tricuspid valve. The septal leaflet was abnormal, with thickening and mild fibrosis particularly at the base near the defect (Fig. 3). The defect was closed with interrupted sutures. Attached to the undersurface of the septal leaflet of the tricuspid valve was an aneurysm of the membranous septum, with no communication with the right ventricle. The aneurysm was closed at its base with running sutures. The patient had an uneventful postoperative course.

DISCUSSION

Left ventricular-right atrial communication is a rare lesion, several autopsy studies revealing an incidence of 0.08% of all congenital heart defects (Laurichesse *et al.*, 1964). There is a slight preponderance of females over males (Riemenschneider

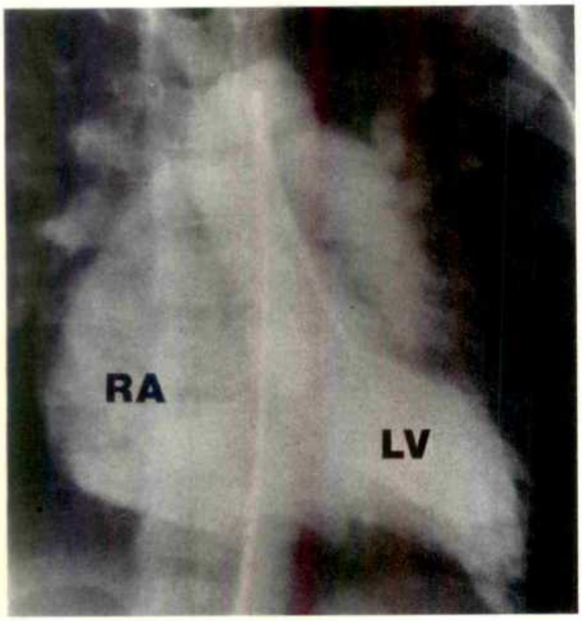


FIG. 2A.
Dense opacification of the right atrium (RA) from the left ventricle (LV), during systole.

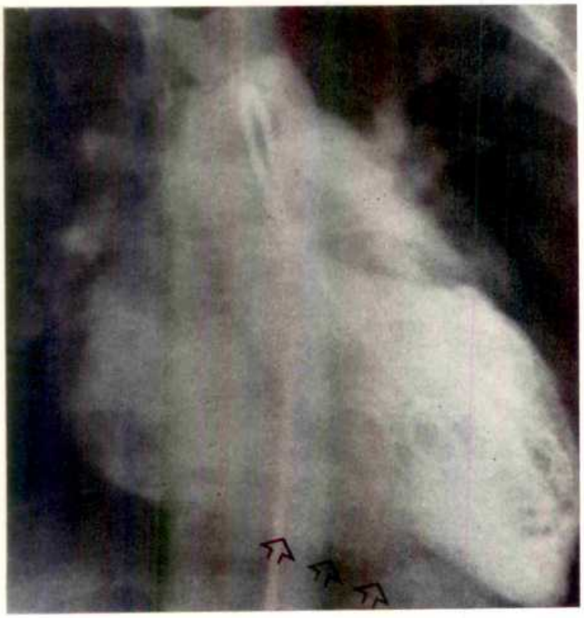


FIG. 2B.
The right ventricle (arrows) opacifies during ventricular diastole from the right atrium.

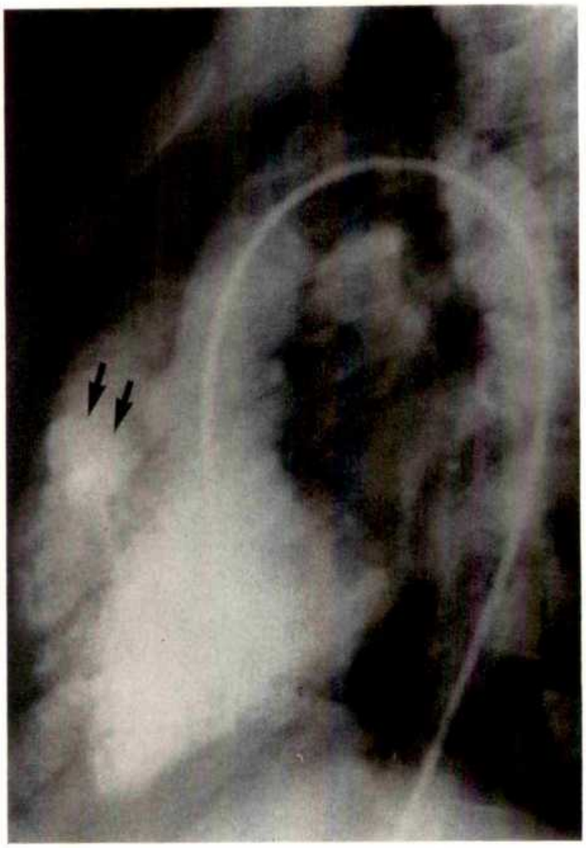
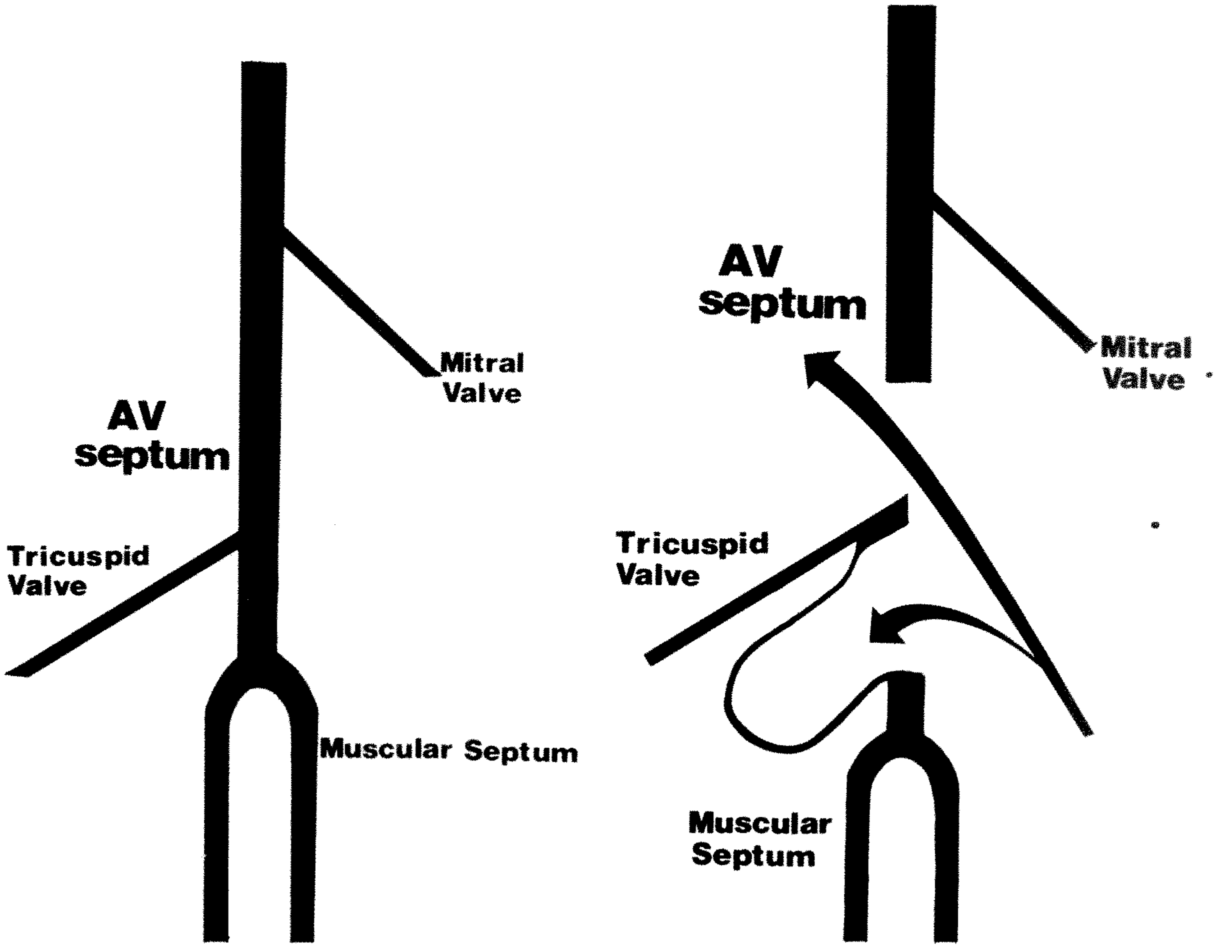


FIG. 2C.
Lateral film clearly demonstrates a large aneurysm of the membranous septum (arrows).

and Moss, 1967). The average age at the time of diagnosis is ten years. The diagnosis of a left ventricular to right atrial shunt should be inferred from the combination of physical findings suggesting a ventricular septal defect and an increase in oxygen content in the right atrium at catheterization. Right atrial pressures are characteristically normal, with the right atrium and vena cava apparently acting as a pressure reservoir. A moderate increase in pulmonary artery pressure is noted in about 50% of the reported cases. Electrocardiographic disturbances, especially conduction delays, have been reported in association with this lesion.

Left ventriculography is the best method of diagnosing left ventricular to right atrial shunt. However, when there is evidence of biventricular enlargement with marked right atrial dilatation, overcirculation, and a relatively small aortic arch, the diagnosis may be suggested (Elliot *et al.*, 1965, and Kramer and Abrams, 1962). This case, however, did not exhibit these changes.



A B

FIG. 3.

(A) Normal relationship of the septal leaflet of the tricuspid valve to the atrioventricular and interventricular portions of the membranous septum. (B) Communication between the left ventricle and right atrium at the atrioventricular septum level (long arrow); note aneurysm of the interventricular membranous septum attached to the undersurface of the septal leaflet of the tricuspid valve (short arrow).

Although first described by Thurnam, 1838, and Buhl, cited by Meyer, 1857, preoperative diagnosis was first made in 1960. Since then several more angiographically proven cases have been reported, but none in association with an aneurysm of the interventricular septum. This association of a left ventricular-right atrial communication and an aneurysm of the membranous septum attached to the under-surface of a thickened septal leaflet of the tricuspid valve suggests the possibility that these anomalies are secondary to defective development of the primitive mesenchymal cells completing the formation of the membranous septum, unlike forms of persistant atrioventricular canal which result from failure of fusion of the endocardial cushions (Wakai and Edwards, 1956). It is possible that the aneurysm found in our case represents the healing phase of a previously patent ventricular septal defect. Aneurysm formation has been postulated as a mechanism for spontaneous closure of uncomplicated interventricular septal defects (Varghese and Rowe, 1969; Misra *et al.*, 1970; Lambert *et al.*, 1974; and Freedom *et al.*, 1974).

The existence of an aneurysm of the membranous septum as well as a direct left ventricular-right atrial communication suggests that the aneurysm may represent a healing phase of a previously patent ventricular septal defect at that location, with sealing of an interventricular communication leaving the purely ventricular-to-atrial flow present in this case.

1978, *British Journal of Radiology*, *51*, 466–469

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Ceco-sigmoid volvulus – a new entity?

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Compound volvulus, that is, volvulus or intertwining of two separate loops of bowel, is exceedingly rare. Twisting of the ileum around the sigmoid is a well-known type of compound volvulus and is known as the "intestinal knot syndrome". This report deals with twisting of the caecum and sigmoid colon around each other. It is believed to be the first case in the world literature of this condition.

Case Report

A 35-year-old white female presented with acute onset of abdominal pain of one day's duration, associated with nausea and vomiting and no flatus or stool since the onset of the pain. One year previously a uterine fibroid had been excised, this being her only abdominal surgery.

On examination the patient was in severe pain, with acute tenderness to palpation in the left iliac fossa. Admission abdominal film (Fig. 1) showed a large, centrally situated, gas-filled loop of bowel. There was no evidence of small bowel distension.

A diagnosis of caecal volvulus was made and a barium enema performed (Figs. 2 and 3). Barium came to an abrupt halt in the sigmoid colon with a beaking appearance to the leading edge. No barium could be induced to flow past this

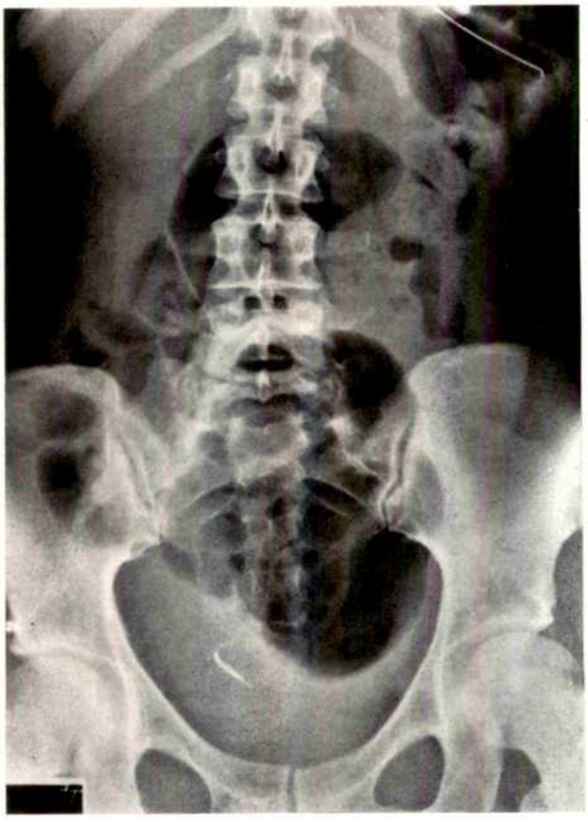

Fig. 1.

There is a large centrally situated gas collection consistent with a dilated abnormally situated caecum.

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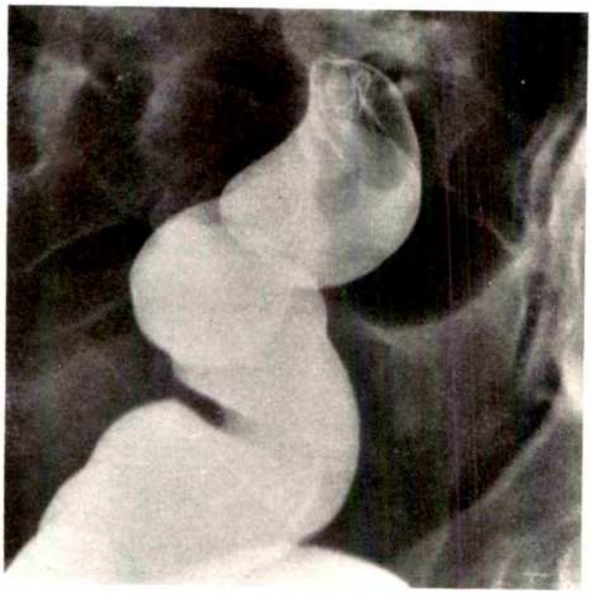

FIG. 2.

Abrupt termination of barium column in sigmoid with tapering appearance consistent with sigmoid volvulus.

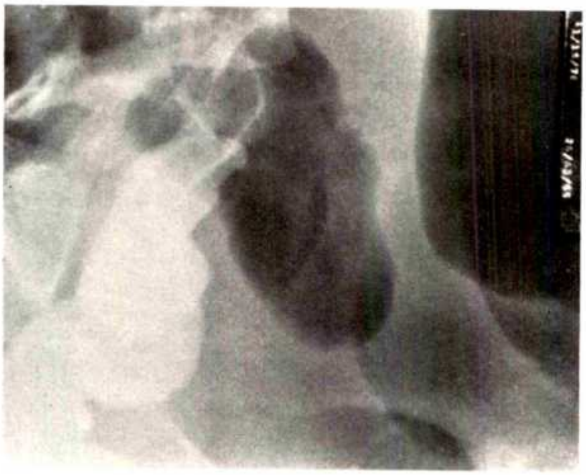

FIG. 3.

Oblique views again shows truncated appearance of end barium column with intimate relationship of large gas containing structure.

point despite the administration of Glucagon. The previously noted collection of gas was in close relationship to, but separate from, the end of the barium column. Sigmoid volvulus was diagnosed but no attempt was made to reduce the volvulus at this time as the patient experienced intense pain during the study. There was still no explanation for the large collection of gas which did however appear to be within bowel.

A rectal tube was passed without result and a few hours later a repeat limited barium enema was performed in an

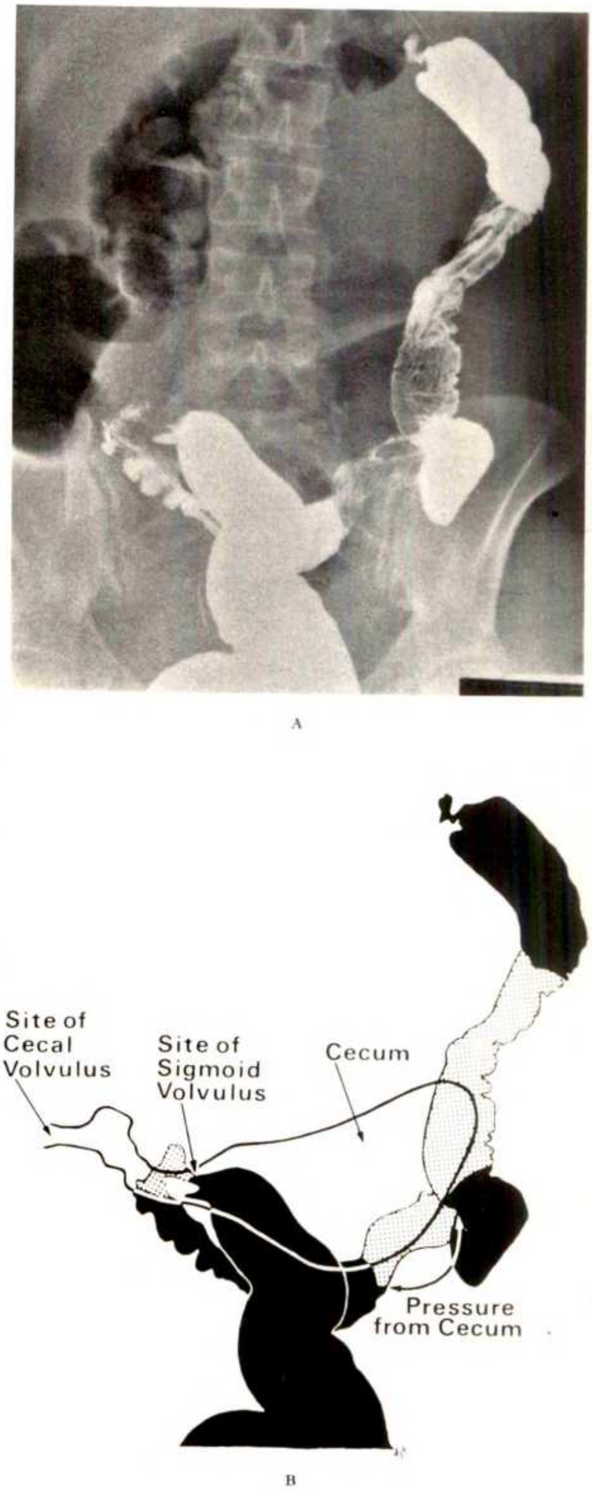

FIG. 4.

Barium has passed beyond the site of obstruction and the large gas collection is seen to be causing an extrinsic pressure defect on the descending colon and proximal sigmoid.

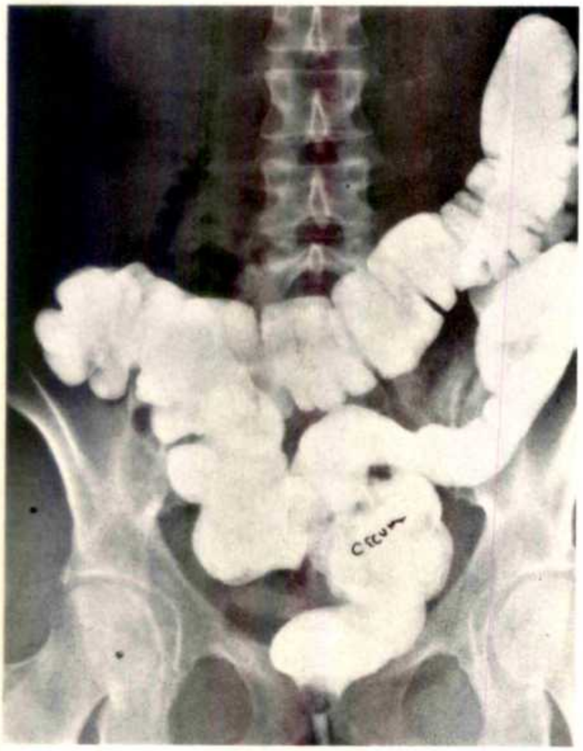

FIG. 5.

The anatomical relationship of the caecum to the sigmoid colon following reduction and settling of patients symptoms are shown—caecum low in pelvis and in left iliac fossa.

attempt to reduce the "sigmoid volvulus". This was successful (Figs. 4A and 4B) and barium now flowed beyond the previous site of obstruction where, however, there was residual narrowing. More proximal in the sigmoid there was an extrinsic pressure defect which appeared to be caused by the large gas collection.

At this stage the diagnosis remained sigmoid volvulus; however, there was still no real explanation for the large gas shadow which still appeared to be compatible with a dilated caecum. Over the next few hours the patient's pain and tenderness settled and her general condition gradually improved. It was decided to perform elective surgery one week later and a limited barium enema was performed to show the anatomy before surgery. The colon was very redundant with the ascending colon situated more medially than normal and the caecum situated low in the pelvis and extending almost to the left iliac fossa. At this stage the gas shadow had resolved (Fig. 5), but its previous position and outline corresponded to a caecum dilated and displaced from the left iliac fossa into the mid-abdomen (as would occur in volvulus).

At surgery the sigmoid was redundant with a relatively long mesentery. The caecum was freely mobile with a long mesentery and was situated in the left lower quadrant. It was large, with oedematous walls, and there was neovascularization of the serosal surface. At the junction of the caecal mesentery and the terminal ileum there was an area of inflammation associated with adhesions. The small bowel appeared completely normal.

Caecopexy and sigmoidpexy were performed to prevent recurrence of the volvulus.

DISCUSSION

Volvulus of various parts of the colon is not rare and is a not insignificant cause of intestinal obstruction with an estimated range from 10% in USA to 30% in eastern European countries. In Iran it is estimated that volvulus is the cause of 80% of colonic obstructions. The most common sites to be involved in simple volvulus are the sigmoid colon and the caecum in that order of frequency. Much less common sites to be involved are the splenic flexure and the transverse colon. The basic anatomical requirement for a volvulus to occur is a long mesentery allowing abnormal mobility and a short attachment of the base of that mesentery allowing twisting around the base.

Compound volvulus or intestinal knot formation involving the intertwining of two loops of bowel is much less common. This condition is exceedingly rare in the USA the majority of cases having occured in Africa (Shepherd, 1967; White and Palmer, 1963), Iran (Vaez-Zadeh and Dutz 1970), Finland and Russia (Kallio, 1932).

Kallio reviewed the literature in 1932 and found 161 cases of intestinal knot, of which 150 (93%) were from Finland or Russia. A more recent discussion (North and Weens 1964) added three more cases of intestinal knot and stressed that the majority of cases are males in the 50–60 age group. Uncomplicated caecal volvulus is a disease of the 20–40 age group with female predominance. Sigmoid volvulus is more common in the 60–70 age group, predominantly in males. There is an increased incidence in mentally retarded or disturbed patients and geographic differences as have been mentioned, thought to be associated with differences in dietary intake.

Three types of compound volvulus have been described before (Kallio 1932, Frimann-Dahl 1942); ileosigmoid, ileoileal and the extremely rare ileocaecal. Knots may also form between the ileosigmoid and either the appendix or a Meckel's diverticulum (Mikal and Byers, 1956), but the basic pathology here is thought to be inflammation followed by adhesions and subsequent torsion and is therefore not included in the classification.

Frimann-Dahl (1942; 1974) elucidated the radiological findings to be expected in intestinal knot, namely a distended sigmoid loop in the right abdomen and multiple loops of small bowel in the left abdomen with multiple air fluid levels. On barium enema the picture may look like uncomplicated sigmoid volvulus except that on the lateral view with barium there is a long curved offshoot explained by some barium having penetrated into the knot.

The present case does not fit into the previously described types of intestinal knot as the compound volvulus involved twisting of the caecum and sigmoid around each other. Because it is so unusual the case posed a number of difficult problems diagnostically. The admission film was consistent with caecal volvulus, the central collection of gas being compatible with a dilated caecum displaced from the normal position in the right iliac fossa into the mid abdomen. It was most surprising therefore to find on barium enema complete obstruction to flow in the sigmoid, the configuration indicating sigmoid volvulus.

The surgical findings support the diagnosis of prior volvulus involving twisting of the caecum and sigmoid around each other. Both the caecum and sigmoid had long mesenteries and the caecum especially was free floating, low in the pelvis and had multiple areas of inflammation of the caecal mesentery at the site of torsion and residual oedema of the caecal walls presumably due to vascular compromise.

This case is also unusual for a complicated volvulus in that the repeat barium enema resulted in untwisting of the condition, whereas the classical course in complicated volvulus is usually rapid and progressive deterioration. This is thought to be caused by the vascular compromise that results from the tight and multiple knotting of ileum around the other loop of bowel involved. Here the caecum and sigmoid presumably did not form that type of tight knot, but instead formed a single loose knot which was relatively easily untwisted.

This condition presumably could only occur with the simultaneous predisposing factors of a long sigmoid mesentery and an abnormally situated caecum also on a long mesentery.

ACKNOWLEDGMENTS

Many thanks to Miss Debra Sharpe for typing this manuscript and to Miss Deborah Hansen for the line drawing.

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Leiomyosarcoma of the oesophagus with dense calcification

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(*Received July, 1977*)

Leiomyosarcoma is a rare neoplasm of the oesophagus (Rainer and Brus, 1965). Surgical resection offers a good prognosis in contrast to that of oesophageal carcinoma. We have recently had the opportunity to examine a patient with leiomyosarcoma showing a densely calcified mass in the mediastinum as well as a polypoid defect in the adjacent oesophagus. The former was noticed four years previously and remained almost unchanged while the latter rapidly increased in the course of one and a half years. The purpose of this paper is to describe the radiographic findings of a calcified leiomyosarcoma and to indicate the possibility of malignancy even in a densely calcified and non-growing mass.

CASE REPORT

A 43-year-old Japanese woman was referred to Tokyo University Hospital with a two year history of progressive dysphagia. A densely calcified mass was seen in the upper mediastinum on chest X ray four years previously.

A barium swallow 18 months previously was interpreted as showing oesophageal compression by the calcified mass. Retrospectively, however, a small polypoid tumour was visible in the cervical oesophagus at the level of the calcified mass (Fig. 1).

A barium swallow on this admission demonstrated a large polypoid defect in the upper third of the oesophagus (Fig. 2). The base of the tumour was adjacent to the calcified mass which was oval in shape with a rather smooth border. Endoscopic study confirmed a large intraluminal tumour with an irregular surface in the cervical oesophagus. The biopsy specimen was interpreted as a leiomyosarcoma.

At operation the calcified mass was connected to the oesophageal lesion; histologic examination showed both masses to be leiomyosarcomas with microscopic calcification in the intraluminal mass.

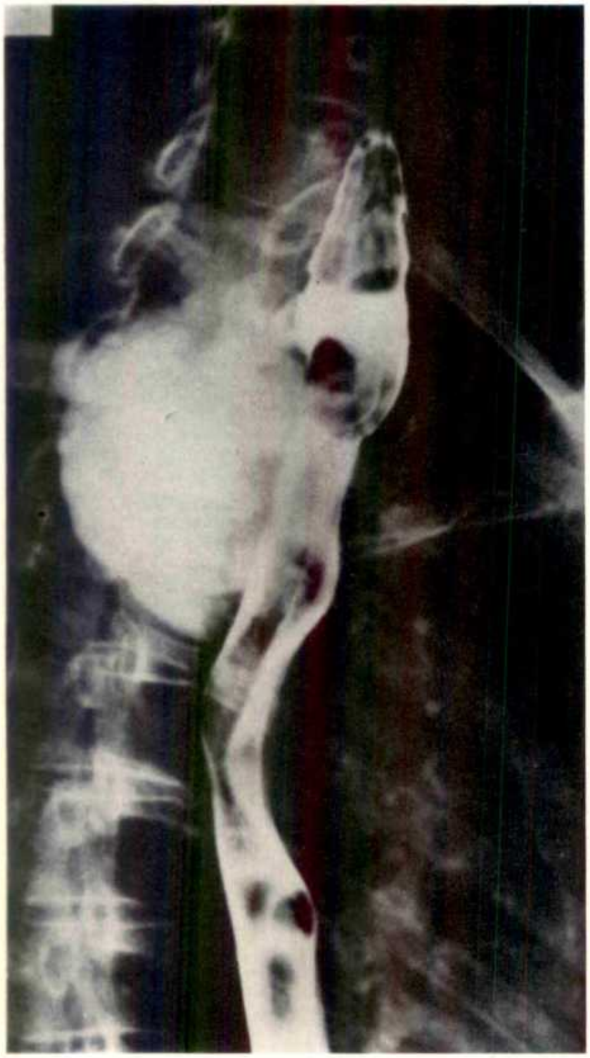

FIG. 1.
Oesophagogram: Dense calcified mass as well as polypoid defect in the cervical oesophagus were revealed.

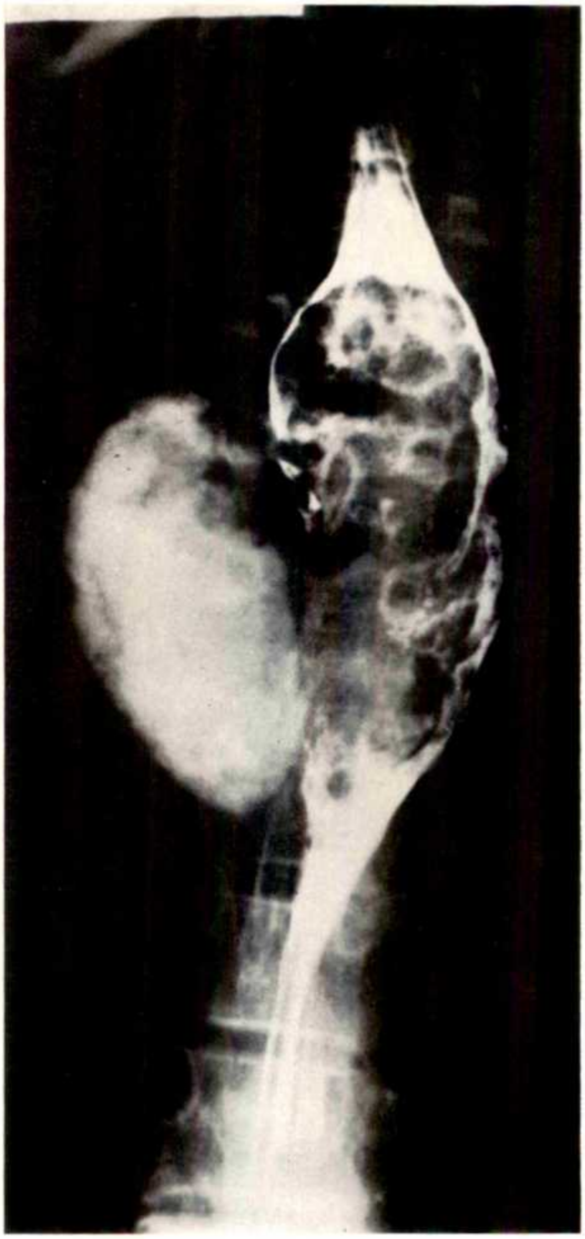

FIG. 2.
Oesophagogram taken one-and-a-half years later. Large intraluminal tumour was noticed adjacent to the calcified mass.

DISCUSSION

Calcification in a leiomyoma is occasionally seen but it is rare in those cases occurring in the oesophagus (Huddy and Griffiths., 1972). Gutman (1972) reported a case of oesophageal leiomyoma with posterior mediastinal calcification and noted that two cases had been previously reported in 75 proven leiomyomas of the oesophagus. The radiographic appearance of the calcification may be circumscribed, stippled, patchy or amorphous. Calcification of a leiomyosarcoma detected *in vivo* has been only sporadically reported (Klion, 1970). In 33 cases of oesophageal leiomyosarcoma reviewed by Rainer and Brus, (1965), calcification was not mentioned at all. However, it was reported that the rate of microscopic calcification is not different in leiomyoma and leiomyosarcoma of the small intestine (Starr and Dockerty, 1955). The presence of dense calcification in the mediastinum should not exclude the possibility of oesophageal malignancy.

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The Institute Awards

The British Institute of Radiology makes a number of awards every year. There are two memorial lectures (in memory of Silvanus Thompson and Mackenzie Davidson) which include the award of a bronze medal and an honorarium. The lectureships are awarded respectively to distinguished non-medical and medical workers in radiology or allied subjects, from the United Kingdom or abroad. These lectureships are not limited to members of the Institute.

Every third year the Institute makes the Stanley Melville Memorial Award to one of the younger members of the Institute. Its purpose is to enable the recipient to visit clinics and institutions abroad. In addition the Institute sponsors annual visits by younger members to hospitals in Sweden by a diagnostician and to hospitals in Paris by a radiotherapist.

The Institute makes three awards every year for distinguished contributions to The British Journal of Radiology. The Barclay medal can be awarded to anyone, member or non-member of the Institute, whose contributions over a period of years have been of especial merit and have contributed materially to the advancement of any aspect of radiology.

Only members of the Institute (or teams containing at least one member) are eligible for the Barclay and Röntgen prizes. They are awarded for contributions to the journal which have been of especial merit. The Barclay prize is awarded for contributions in diagnostic radiology or physics or other experimental work related to diagnostic radiology. The Röntgen prize is similar but is awarded for contributions in the field of radiotherapy or related studies in radiobiology or physics.

Awards for 1978

This year the Barclay prize was awarded to **Dr. Louis Kreel** of Northwick Park Hospital for his important contributions to the radiological study of the liver, spleen and pancreas and for his work on computerized whole body tomography.

The Barclay medal has been awarded to **Professor Tubiana** of the Institut Gustave Roussy, Paris, for his distinguished contributions to the British Journal of Radiology in the fields of radiotherapy and radiobiology.

The Röntgen prize has been awarded to **Dr. David Greene** of the Christie Hospital and Holt Radium Institute for his many excellent contributions to The British Journal of Radiology in the field of physics applied to radiotherapy.

1978, *British Journal of Radiology*, *51*, 472

Short communication

X-ray dose received by patients in a population survey for colonic diverticular disease

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In recent years there has been a considerable interest in the hypothesis that diverticular disease of the colon is a deficiency disorder due to lack of fibre in the diet. To test this idea a method for the diagnosis of diverticular disease had to be found which was both feasible for epidemiological work and which conformed to the guidelines for research projects involving radiation to human subjects proposed by the World Health Organization (BIR Bulletin, 1975). The only reported method (Manousos *et al.*, 1967) partially fulfilled the first requirement but perhaps not entirely the second by today's standards. Based on that technique, a barium follow-through method is now described which meets both criteria.

Method

For the purpose of this study, a method was sought which would allow two and occasionally three radiographs of the abdomen to be performed with safety. The World Health Organization guidelines indicate that a Category I project should result in an individual not receiving more than 0.05 rem total body dose and not more than 0.25 rem to any single organ. This dose is considered to be within the variations of natural background which may be received by individuals during the period of one year.

The technique used to radiograph the abdomen was as follows. The X-ray tube target to table-top distance was 117 cm. The table-top to film distance was 8 cm. 115 kV was used, filtration 2.5 mm aluminium equivalent. An exposure of 3.2 mAs was adequate for a subject thickness of 22 cm. A 35 × 43 cm cassette was used with the beam of radiation collimated to just cover the cassette, the beam at table-top level being 32 × 40 cm and the skin area irradiated being approximately 850 cm^2. The exposure without back scatter was on average 65 mR using fast film, Kodak RPL, with either Ilford rare earth intensifying screens or Dupont barium fluorochloride screens. The two screens appeared to be identical in speed and quality for this purpose.

For three films the skin exposure was, therefore, 195 mR or, say, 250 mR with back scatter. This falls within the maximum single organ dose of 0.25 R since any critical organ will be at depth and receive a smaller dose. The superficial organs would be unlikely to receive an average dose of more than 25% of the skin exposure and deep organs more than 10%. The R cm^2 value for three films would be less than 200 R cm^2. The total energy of this radiation leaving the tube port would be approximately 20 g rad per R cm^2 if all were to be absorbed in the individual (Marshall, 1976). It was estimated that approximately 35% would be lost in back scatter, side scatter and exit beam, resulting in 13 g rad/R cm^2 being absorbed in the field irradiated and in the individual towards the head or feet. For the 200 R cm^2 required for three films, this would be an integral dose of approximately 2.6 kg rad. If a standard man of 70 kg received uniform whole body radiation up to 0.05 rem, as suggested by WHO Category 1, this would result in an integral dose of 3.5 kg rad. It is considered, therefore, that with this technique three radiographs of the abdomen can be taken well within a Category 1 project.

A combined validity trial and pilot study was carried out using 27 subjects including 10 cases of diverticular disease proved by barium enema. The 10 known cases had a preliminary radiograph of the abdomen to ensure that there were no traces of the previous barium enema. All subjects were then instructed to take three doses of 40 ml of barium sulphate (Baritop 100) at intervals between 108 and 96 hours prior to X-ray examination. No dietary restrictions whatsoever were placed on the subjects. Each subject then had a supine radiograph of the abdomen as described. The known diverticular patients thus had two films for this investigation. Only two of the seventeen volunteers had to have a second film taken because the first showed that the barium had not yet passed the whole length of the bowel. The radiographs were assessed by two independent radiologists. All ten positives were identified plus two extra from the volunteer sample.

The main study on the incidence of diverticular disease in volunteers with different dietary habits, to be reported subsequently, has not involved an exposure of more than 9 mAs to any one in the first 300 individuals, most only requiring one film, and thus the radiation exposure fell well within WHO Category 1 limits.

Acknowledgments

We would like to thank the Medical Research Council who have largely funded the main project and Concept Pharmaceuticals for supplying the barium sulphate.

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1978, *British Journal of Radiology*, *51*, 473

JUNE 1978

Correspondence

(The Editors do not hold themselves responsible for opinions expressed)

NSD, CRE, TDF and SI units

THE EDITOR—SIR,

The concepts of nominal standard dose (NSD) and cumulative radiation effect (CRE) are now well accepted in radiation therapy. The unit of NSD is ret (rad equivalent therapy) and the number of rets for various fractionation schedules have been published (Phelps and Phelps, 1974). With the introduction of SI units in radiology and the requirement that the special units of radiation be phased out within a period of ten years, it will be necessary that the unit ret should also be replaced. As gray (1 Gy = 100 rad) is the SI unit of absorbed dose, the corresponding unit of NSD may be called get (gray equivalent therapy), and

$$1\ \text{get} = 100\ \text{ret}$$

The unit of CRE, namely reu (radiation effective unit), has the same dimension as ret and it is also seen by definition (Kirk *et al.*, 1971) that

$$1\ \text{get} = 100\ \text{reu}$$

This implies only that the magnitudes of NSD given in rets or CRE given in reus in tables used at present will have to be reduced by a factor of 100 to convert them into gets. For example, a typical NSD value of 1800 ret will be equivalent to 18 get. The dimension of the new unit will be $\text{J kg}^{-1}\ \text{day}^{-0\cdot11}$ If, however, the units of NSD and CRE are to be given separate identities for the reasons stated by Kirk *et al.*, (1971), a new name may be chosen for the latter. In this case, the unit reu itself may be retained, but with a magnitude 100 times greater than the present value.

This adoption of SI units will also reduce the values of TDF factors (Orton and Ellis, 1973) by a factor of $100^{1\cdot538}$ or 1191. For example, a TDF factor of 101.53 for 1800 ret in special units will correspond to a TDF factor of 8.523×10^{-2} for 18 get in SI units. The dimension of the TDF factor in SI units will be $\text{J}^{1\cdot538}\ \text{kg}^{-1\cdot538}\ \text{day}^{-0\cdot169}$. The NSD and CRE values in this system appear to be convenient for handling while the TDF factors appear to be too small in magnitude.

Yours, etc.,
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Suggested terminology for scanning investigations

THE EDITOR—SIR,

I quite agree with Messrs. Keyes and Mallard (1978) that one should be practical and therefore adopt terminology which both clinicians and radiologists are likely to use. However, to achieve this we need names which are as brief as possible, yet reasonably specific in meaning. Thus I would suggest:

CAT-scan for computerized axial tomography
Iso-scan for radioisotope investigations
Ultra-scan *or* Sonic-scan for ultrasound examinations.

These all seem to trip lightly off the tongue and should not be misinterpreted. No doubt other readers will be able to suggest additions and alterations to this list.

Yours, etc.,
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KEYES, W. I., and MALLARD, J. R., 1978. Nomenclature in scanning investigations, *British Journal of Radiology*, *51*, 61.

Mechanism of radioprotection by vitamin C

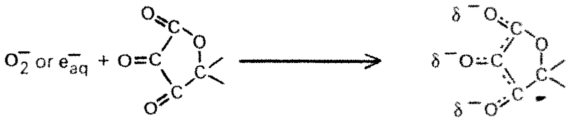
THE EDITOR—SIR,

In their interesting paper on a radioprotective effect of vitamin C, O'Connor *et al.* (1977) express uncertainty as to the mechanism of the effect but suggest that radical scavenging should be considered. I would like to suggest that the related mechanism of electron scavenging is more probable.

X rays produce radiation damage by a process of ionization; molecules are disrupted to form ion pairs, and one member of each pair will normally be an electron. Some of the electrons released in the tissue have considerable initial energy but all, eventually, will lose energy until they can combine with molecules or become "solvated" in a shell of water molecules. At this stage, when the electrons have thermal, or quasi-thermal, energies their properties can be considered in terms of chemical reactions (Dainton, 1975).

In oxygenated tissue, a probable reaction of the solvated electron is to add to a dissolved oxygen molecule to form the superoxide ion, O_2^-. The superoxide ion is known to be reactive and potentially damaging to the tissue in which it is formed; support has been found (Oberly *et al.*, 1976) for earlier suggestions that such damage may be the origin of the oxygen effect.

The conjugated ketone structure of the vitamin C molecule is such that it must be expected to be a most potent electrophore (Lovelock and Gregory, 1962); electron-molecule reactions of the type



must be expected to occur. An ESR signal, which could be due to the formation of radical ions by this process, has been reported to occur in irradiated tissue (Vaughan *et al.*, 1973; Floyd *et al.*, 1973), and *in vitro* work has been demonstrated oxidation of ascorbic acid by superoxide (Nishikimi, 1975; Lee-Ruff, 1977).

I suggest, therefore, that the mechanism of the reported protective effect is due to electron scavenging by ascorbic acid or ascorbate either directly, in competition with dissolved oxygen, or by an electron transfer reaction from the superoxide ion. The resulting reduction in superoxide concentration decreases tissue damage due to toxic concentrations of superoxide and this decrease in damage is the radioprotective effect.

Other radioprotective agents also contain electron accepting groups and may act similarly.

Yours, etc.,
N. L. Gregory.

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Vitamin C and radioprotection

(*In reply*)

The Editor—Sir,

Gregory raises the question of the mechanism through which vitamin C exerts the radioprotective effect observed by us in Chinese hamster ovary cells (O'Connor *et al.*, 1977). The data we presented was such that in its own right it gave no indication of a likely mechanism. Consequently the basis for the effect was considered equally likely to be physiological or chemical. A chemical mechanism was intended to imply a direct interaction between ascorbate and some radiation induced factors in the cell. On the other hand a physiological mechanism was intended to convey a more complex process whereby the cell was altered by the presence of ascorbate in such a way that it was subsequently more resistant when challenged with radiation.

It should be possible to go some way towards distinguishing between chemical and physiological effects through relatively simple experiments designed to determine the time required for the effect to appear. Chemical effects are likely to become evident almost instantaneously as they depend only on the presence of the agent during irradiation. Physiological effects such as those produced by protracted hypoxia (Foster *et al.*, 1971; Alper, 1977) or by Miracil–D (Bases, 1970) may take longer to appear and may be induced by the presence of the agent before or after the irradiation without the necessity for the agent being present during irradiation. Much more sophisticated experiments would be required to distinguish between the two chemical-type mechanisms discussed by Gregory. However, it does appear from his comments and from recent evidence that the protective effect of vitamin C is very likely to be chemical in origin (Biaglow and Jacobson, 1977; Gregory, preceding letter; Redpath and Wilson, 1973).

Regardless of the detail of the mechanism, the evidence presently available demonstrates that vitamin C is a radioprotective agent. This may appear to give rise to a problem when administering high doses of the vitamin to patients undergoing radiotherapy (Cameron and Pauling, 1974) as some tumours have substantially higher levels of vitamin C than surrounding normal tissues (Moriarty *et al.*, 1977 a,b). Therefore it is possible that the tumour may be protected to a greater extent than normal tissue. In the case of hypoxic tumours, however, vitamin C would be unlikely to add to the protective effect of oxygen deficiency since the mechanism underlying both protective states appears to be the inhibition of the formation and/or fixation of free radicals (Redpath and Wilson, 1973; Lett *et al.*, 1967; Chapman *et al.*, 1973). Therefore, with hypoxic tumours, vitamin C could leave the sensitivity of the tumour unaltered while protecting surrounding normal tissue, thereby offering a therapeutic advantage. This is a reversal of the usual procedure undertaken to enhance the therapeutic ratio, in which attempts are made to sensitise the tumour relative to surrounding tissues.

The overall position of ascorbate in relation to radiotherapy requires further study in the light of recent data presented by Biaglow and Jacobson (1977). They reported an interaction between ascorbate and hypoxic-cell sensitizing compounds (*e.g.* Flagyl or Ro–07–0582) leading to oxidation of the ascorbate. This gives rise to the possibility of increased oxygen consumption, which could lead to even greater radioprotection for the tumour and negate the effect of the nitrocompounds. Formation of toxic products is another possibility. This could be beneficial by killing tumour cells or deleterious by leading to side effects such as neurotoxicity (Fowler *et al.*, 1976).

Therefore in view of all the possible interactions between vitamin C, nitrocompounds and radiation, it is evident that the vitamin needs careful scrutiny under a variety of conditions before its proper place in the management of radiotherapy patients can be determined.

Yours, etc.,
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Lead aprons and film badges

THE EDITOR—SIR,

I have read with interest the questions raised by your correspondents Dr. Bray and Dr. Sear whether a film badge should be worn over or under a protective lead apron.

The key point is that if the film badge is worn on top of the apron then it will greatly overestimate the exposure received by the user. The answer is not simple.

The United States Nuclear Regulatory Commission in Title 10 Code of Federal Regulations, Part 20 (10 CFR 20) states that any individual in a restricted area in any period of one calender quarter should not be exposed to a dose in excess of 1.25 rem to the following part(s) of the body: whole body, gonads, active blood-forming organs, head and trunk, lens of eye.

It is not true that by wearing the film badge on the collar the exposure to the head and trunk could be measured. The permissible limiting factor is the exposure to the eyes. To determine that this is not exceeded, some authorities recommend wearing the film badge on the collar or attaching it to eye glasses. Neither of these answers is totally satisfactory where an active person is involved, but some state regulatory agencies are requiring this. The wearing of the film badge under the apron is likewise a less than desirable choice as it underestimates eye exposure by significant quantities. Hence the answer is not simple. One practical solution to this problem which may not be acceptable to others for aesthetic reasons is to wear the film badge on the forehead using a head band or if it is a TLD chip it could be placed on the forehead using a temporary adhesive, as a Tilak (beauty spot) worn by Indian ladies for aesthetic and cultural reasons.

Yours, etc.,
I. B. SYED.

Medical Physics Division,
Department of Radiology,
Baystate Medical Center,
Springfield, MA 01105, U.S.A.

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Alterations in the manuscript of Röntgen's publication "Ueber eine neue Art von Strahlen" (1895)

THE EDITOR—SIR,

Reading F. Freund's article "Lenard's share in the discovery of X-rays" in the 1946 issue of your Journal, I was struck by a passage that opposes Röntgen's statement that he had made his discovery when experimenting with a Hittorf tube. The passage reads: ". . . it can be reasonably assumed that he [Röntgen] experimented with a Lenard tube, when on November 8, 1895, a barium platinocyanide screen was lying at a distance beyond the range of cathode rays and started to fluoresce. This assumption can be confirmed by Rontgen's (1895) original manuscript 'A New Kind of Rays'. He writes: '. . . and covered the Lenard apparatus with a tightly-fitting coat of thin cardboard. . .', but crossed 'Lenard apparatus' out and wrote instead 'the tube'. . ."

The only author who seems to have contradicted this view was Etter (1946), when he commented that this "hardly proved that Röntgen used the Lenard tube exclusively".

In my opinion one can disagree with Freund (1946) on the much firmer ground that the change in the manuscript was never made in the form Freund assumed.

I came to my conclusion on consulting a reproduction of the first page in question (Fig. 1). Careful inspection of the correction in the fifth line led to the following observations:

(1) The last of the three crossed-out words, to which Freund refers, is unmistakably "Apparat".

(2) The preceding crossed-out word, which according to Freund might have been "Lenard'schen", certainly covers not more than 15 mm, whereas the word "Lenard'schen", as it appears earlier in the text, has a length of 26 mm.

(3) The only remaining possibility that fits Freund's theory is that Röntgen wrote "Lenard Apparat" ("Lenard" having the correct length), but this would imply a rather strong deviation from normal German usage.

(4) The still visible part of the first letter of this crossed-out word shows more resemblance to the capital E, as it occurs in the manuscript, than to the capital L.

(5) In my opinion Röntgen first started to write "den Entladungsapparat", but broke off before the letter g was written. He may have done so, because he realized at this point that he had used the word "Entladungen" in the previous line. So he crossed out the unfinished word "Entladun" (having a length of about 15 mm) and wrote instead "Apparat". Then realizing that the word "Apparat" had also been used nearby and might in addition confusingly refer to the "Rumkorff", he crossed out "den Apparat" and finally wrote down "die Röhre".

I conclude that the considered alterations made by Röntgen in his manuscript serve no other than stylistic purposes, and quite tally with the classical conception of his article, in which the style was to match the beauty of his discovery.

Yours, etc.,
E. FISCHMANN.

Philips Research Laboratories,
Eindhoven, Holland.

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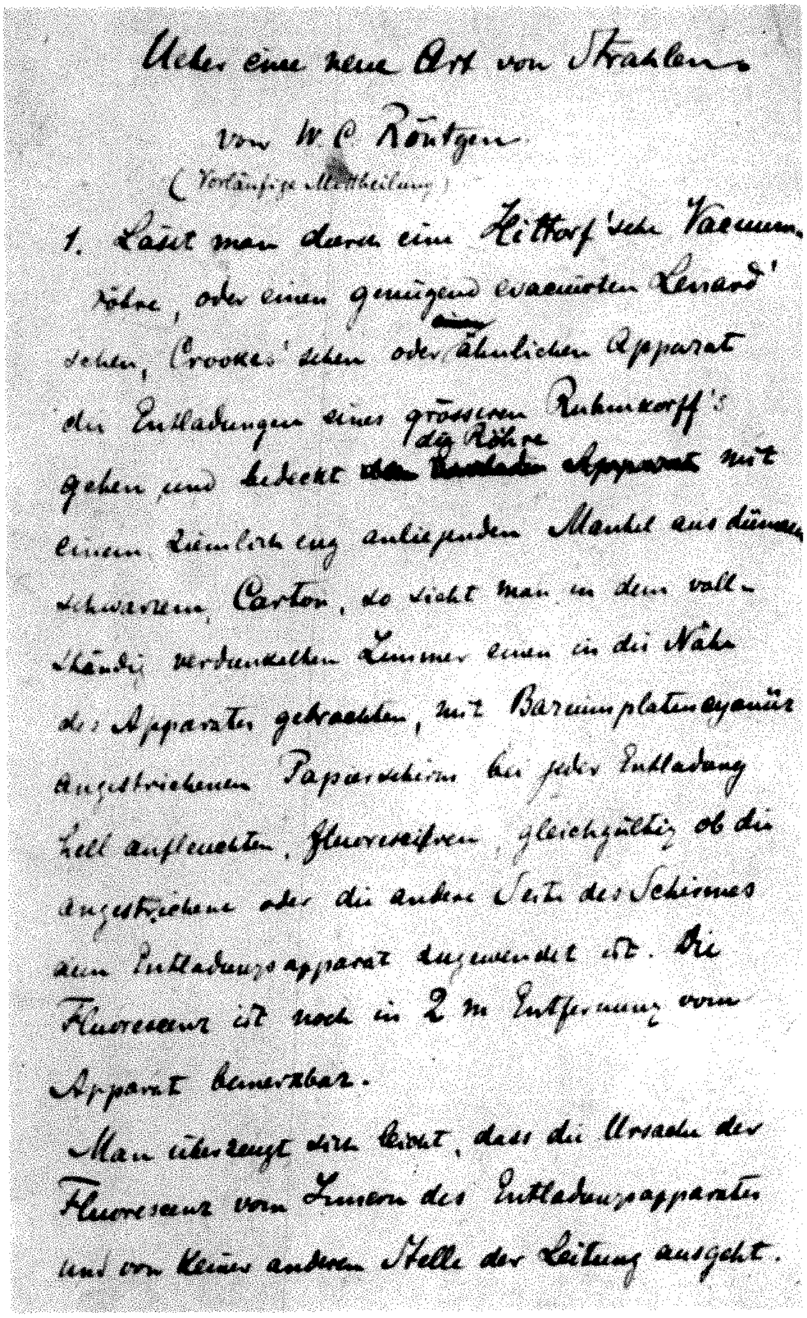
(*illustration overleaf*)



Ueber eine neue Art von Strahlen
von W. C. Röntgen
(Vorläufige Mittheilung)

1. Lässt man durch eine Hittorf'sche Vacuum-
röhre, oder einen genügend evacuirten Lenard'
schen, Crookes'schen oder ~~ein~~ ähnlichen Apparat
die Entladungen eines grösseren Ruhmkorff's
gehen und bedeckt ~~den~~ ~~Entladun~~ ~~Apparat~~ die Röhre mit
einem ziemlich eng anliegenden Mantel aus dünnem
schwarzem Carton, so sieht man in dem voll-
ständig verdunkelten Zimmer einen in die Nähe
des Apparates gebrachten, mit Bariumplatincyanür
angestrichenen Papierschirm bei jeder Entladung
hell aufleuchten, fluoresciren, gleichgültig ob die
angestrichene oder die andere Seite des Schirmes
dem Entladungsapparat zugewendet ist. Die
Fluorescenz ist noch in 2 m Entfernung vom
Apparat bemerkbar.
Man überzeugt sich leicht, dass die Ursache der
Fluorescenz vom Innern des Entladungsapparates
und von keiner anderen Stelle der Leitung ausgeht.

Fig. 1.

The first page of the manuscript of Röntgen's publication "Ueber eine neue Art von Strahlen" (Courtesy of Deutsches Röntgen-Museum, Remscheid, W. Germany). The second crossed-out word in the fifth line is in my opinion the unfinished word-fragment "Entladun" (from "Entladungsapparat"), and not "Lenard", as has been suggested.

1978, *British Journal of Radiology*, *51*, 477 JUNE 1978

Proceedings of the Royal College of Radiologists*

Abstracts of papers presented at a meeting of the Royal College of Radiologists on February 18, 1977 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG

Spontaneous regression of metastases from testicular tumours—a report of six cases from one centre, by C. I. V. Franklin.
A controlled prospective study of thyroid hormonal changes and hypothalamic/pituitary/thyroid axis changes in the first three weeks of a course of radiation therapy, by M. J. Moriarty (*no abstract received*)
Bilateral incidence of testicular tumours, by M. Sokal and M. J. Peckham.
When and how should we teach the basic concepts of radiation beam dosage?, by T. B. Brewin.

SPONTANEOUS REGRESSION OF METASTASES FROM TESTICULAR TUMOURS—A REPORT OF SIX CASES FROM ONE CENTRE

By C. I. V. Franklin†

Christie Hospital and Holt Radium Institute
Manchester

In a review of the cases of testicular tumour treated at the Christie Hospital between 1961 and 1974, there were six cases of spontaneous regression of metastases which are now reported.

In this period, 827 cases of testicular tumour have been treated, giving an incidence of spontaneous regression of 0.72%, which is considerably higher than previously reported. One of the cases appeared to be pure seminoma and spontaneous regression of metastases from seminoma has not been reported previously.

Full paper submitted to *Clinical Radiology* (in press).

BILATERAL INCIDENCE OF TESTICULAR TUMOURS

By M. Sokal and M. J. Peckham

Royal Marsden Hospital and Institute of
Cancer Research Sutton, Surrey

Twenty-two men with bilateral germ cell tumours of the testis have been treated at The Royal Marsden Hospital between 1952 and 1976. The interval between the first and second tumours ranged from nil (in two men who presented with disease simultaneously in both testes) to 15 years. Testicular maldescent was three times as common in this group compared with other series describing testicular neoplasms. Treatment for the second tumour was carefully individualized, ranging from orchidectomy alone to a combined surgical, radiotherapeutic and chemotherapeutic approach. 55% of the patients are alive five years after their second orchidectomy. Patients with testicular tumours should be put on long term follow-up. At each visit, the remaining testicle must be carefully examined.

WHEN AND HOW SHOULD WE TEACH THE BASIC CONCEPTS OF RADIATION BEAM DOSAGE?

By T. B. Brewin

Glasgow Institute of Radiotherapeutics and Oncology
Western Infirmary, Glasgow G11 6NT

The amount of difficulty that many trainees, including those medically qualified, have in achieving a sound working grasp of certain basic principles of radiation beam dosage, is often underestimated. Since any failure of understanding may seriously impair the efficiency of the team treating the patient, the discussion of these problems (and especially the monitoring of the results of such discussion by means of oral and written tests) deserves a high priority. Contrary to traditional practice, there would seem to be no good reason why teaching of radiation beam dosage, and the effect on dose rate of changes in the treating distance or in the amount of scattered radiation, should not begin in the very first week of training, and be immediately integrated with discussion of the dose rate information available at every radiotherapy unit when the patient is treated. A preliminary course of physics lectures does not usually make the understanding of these principles any easier and can be done either concurrently or later. For many radiotherapy trainees and for many doctors in other fields, comparsion with drug dosage and with the brightness and scatter of ordinary light beams, avoiding technical terms so far as possible, may achieve a better initial understanding of basic principles than is achieved by mathematical equations and theoretical physics.

This paper was published in full in *British Journal of Radiology*, *50*, 430–434.

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†Present address: The Queensland Radium Institute, Brisbane Q. 4029, Australia.

1978, *British Journal of Radiology*, *51*, 478

Proceedings of The British Institute of Radiology

Unorthodox approaches to fractionation

Abstracts of papers presented at a joint meeting of the Royal College of Radiologists, the Royal Society of Medicine (Section of Radiology) and the British Institute of Radiology held on Friday, February 18, 1977 at The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG

Low dose rate irradiation of advanced head and neck cancers: present status, by B. Pierquin, W. Mueller and F. Baillet.
A low dose fractionation scheme in radiotherapy of oral and bladder carcinoma, by B. Littbrand.
Radiobiological consideration in unconventional fractionation regimens, by R. Withers.

LOW DOSE RATE IRRADIATION OF ADVANCED HEAD AND NECK CANCERS: PRESENT STATUS

By B. Pierquin, W. Mueller, and F. Baillet

Commission de Carcinologie, Service de Radiotherapie, Hospital Henri Mondor, Créteil, France

Forty-six patients with advanced epidermoid carcinomas of the head and neck have been treated with semicontinuous low dose rate cobalt teletherapy with curative intent. The dose rate was 90 to 130 rad per hour, the patients were treated six to eight hours per day, and they received total doses of 6500 to 7000 rad in either single or split course. Thirty-four of these patients have minimum one year follow-up and form the basis of this report. While the survival of these patients was poor (22% at 3 years), the local control rate of 58% was encouraging.

The immediate tolerance of the mucosa was frequently exceeded in single course treatment. Furthermore, there was a high necrosis rate, but skin reactions remained characteristically mild. Split course treatment succeeded in reducing mucosal reactions to a tolerable level, but did not reduce the high risk of necrosis (actually greater than 50% at two years). Residual tumour at three months carried a grave prognosis. All nonsterilizations and recurrences within the low dose-rate treated volumes occurred with tumours 5 cm or more in greatest dimension, while local control was obtained in all ten patients with less extensive primary lesions. Necroses occurred with both the larger and the relatively smaller tumours in equal frequencies. Low dose rate treatment has been proven feasible and is currently being used in a prospective randomized trial to test its possible superiority over conventional fractionation.

A LOW DOSE FRACTIONATION SCHEME IN RADIOTHERAPY OF ORAL AND BLADDER CARCINOMA

By B. Littbrand

Department of Oncology, University Hospital of Umeå, Sweden

Experimental observations indicate a radiation dose-dependency of the enhancement of cellular radiosensitivity by oxygen. This forms the basis of the low dose fractionation scheme designed in an attempt to circumvent the problem presented for radiotherapy by the particular radioresistance of poorly oxygenated malignant cells. Three clinical trials were performed, and the patient was treated according to one of four fractionation schemes. A. 1 G three times a day, five days a week, a total tumour dose of 42 G. B. 2 G once a day, five days a week, a total tumour dose of 40 G. C. 1 G three times a day, five days a week, a total tumour dose of 84 G. D. 2 G once a day, five days a week, a total tumour dose of 64 G. In C and D a split-course technique was used with two to three weeks of rest. The intendent treatment in A and B was irradiation followed by operation of the patients with oral carcinoma.

In C and D the oral and bladder carcinomas were considered inoperable from the outset. The results show that patients treated according to the low dose fractionation schemes (A and C) have an increased clearance rate of the tumour in the mouth and bladder in comparison to the patients treated with the conventional fractionation schemes (B and D). The remaining complications were the same in the different treatment groups indicating an increased therapeutic ratio after the low dose fractionation scheme in comparison with the conventional fractionation scheme.

RADIOBIOLOGICAL CONSIDERATIONS IN UNCONVENTIONAL FRACTIONATION REGIMENS

By H. R. Withers

M. D. Anderson Hospital and Tumor Institute, Houston, Texas

Acute and late effects do not parallel one another when fractionation patterns are changed. Clinical and experimental data show a few large fractions lead to late effects which are more severe (relative to acute effects) than is the case when dose fractions of about 200 rad are given. The reasons for this severity of late effect in slowly- or non-proliferating systems are not known. A net sensitizing effect of division cycle redistribution between dose fractions could increase the acute effect relative to a late effect when large numbers of small dose fractions are used. Also because the cell killing curve is a logarithmic function of dose which increases in steepness with increase in dose while mitotic delay is related linearly to dose, the arrest of cells in G_2-M would be longer and the regeneration during the treatment regimen would be less with a large number of small dose fractions than with a few large ones. Thus, since the critical normal tissues are non-proliferative while the tumour is proliferative, one might expect, from a consideration of the radiobiology of cell proliferation, that the therapeutic ratio would be improved by hyperfractionation and worsened by the use of a few large fractions.

Reprints of these abstracts may be obtained free on application to the Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1.00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (i.e. April for June edition).
Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

WORLD FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY

To be held September 17–21, 1978. The Second International Congress of the World Federation of Nuclear Medicine and Biology will provide an international forum for the exchange of scientific information, the dissemination of knowledge, and the world-wide promotion of the discipline of nuclear medicine.

The Scientific Symposia will encompass all the activities and interests of nuclear scientists and physicians: medical and health physics; instrumentation; data analysis; radiochemistry; radioassays; *in vivo* and *in vitro* biochemical and physiological measurements; radiopharmaceuticals; functions and disorders of the cerebral, pulmonary, cardiovascular, abdominal, renal, peripheral vascular, bone, joint endocrine, and metabolic systems.

There will be three pre-meeting courses: cardiovascular nuclear medicine; positrons, cyclotrons, and tomography; nuclear medicine in developing countries. During the meeting, there will be review teaching sessions on the state of the art in clinical nuclear medicine.

The technologist programme will include considerations of quality assurance, recruitment, education and career opportunities.

The meeting has been designed to afford maximum opportunities for exchanges of ideas and views among nuclear colleagues.

Morning activities will provide a plenary session, time for small discussion groups, and for visiting the exhibits of equipment and radiopharmaceutical manufacturers.

Afternoons will be devoted to contributed papers, poster sessions, panels and mini-symposia.

Further information from Dr. H. N. Wagner, President, WFNMB Second International Congress, 1629 K Street, N.W., Suite 700, Washington, D.C., 20006, USA.

BRITISH MEDICAL ULTRASOUND SOCIETY ANNUAL MEETING AND EXHIBITION

To be held November 27–28, 1978 at the Civic Centre, Newcastle upon Tyne. Potential exhibitors are invited to contact A. J. Hall, Queen Mothers's Hospital, Glasgow, G3 8SH (041-399 8888 ext. 548).

Further details from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

WORKSHOP ON THE USE OF COMPUTERIZED TOMOGRAPHIC SCANNERS IN RADIOTHERAPY

Following the successful workshop meeting on "The Use of Computers in Radiotherapy in Europe", held at the International Atomic Energy Agency in July 1976, the Commission Informatique of the European Association of Radiology will hold a workshop on the "Use of Computerized Tomographic Scanners in Radiotherapy", at the headquarters of the World Health Organization on March 28–30, 1979.

The meeting is designed to promote discussions among therapeutic and diagnostic radiologists, physicists and computer experts with previous experience in this field and will be limited strictly to 150 participants.

The programme will include invited and proferred papers and discussions concerning the recognition and definition of tumour and target volumes and treatment planning as well as future directions for development. The proceedings will be published.

Further information can be obtained from the General Secretary, Professor R. J. Berry, Department of Oncology, The Middlesex Hospital Medical School, London W1P 7PN.

4TH CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY

Will be held in Hamburg, W. Germany, on September 2–9, 1979.

QUANTITATION OF TUMOUR RESPONSE: A CRITICAL APPRAISAL

The the L. H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to simulate a *critical* appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Book review

Use of ionizing radiation and radionuclides on human beings for medical research, training, and non-medical purposes. Report of WHO Expert Committee. Technical Report Series 611, pp. 39, 1977 (World Health Organization, Geneva). Sw. fr 6.00.

This is a clearly and simply written survey of the ethical and other principles which should regulate the use of ionizing radiation (in any of its forms) for purposes other than the direct benefit of a sick person, occupational and incidental (not deliberate) exposure excluded. The recommendations of the WHO Committee which sponsored the report are broadly similar to those of an earlier WHO Committee document which, though still unpublished, has been widely circulated; this new report is likely to be regarded as authoritative because of its WHO imprint.

Radiation exposures for the purposes of medical research are classed into four categories: I about 10 mrem for the whole body, that is well within the variations of natural background from place to place, II about 100 mrem, that is of the same order as natural background, III about 1 rem, that is of the same order as the ICRP annual dose limit for occupational exposure. These dose levels are applicable to single investigations in any one year. Category IV is for other, larger whole-body exposures. When irradiation is limited to particular tissues, as after administration of a radiopharmaceutical, the allowable tissue doses will be increased according to ICRP principles for occupational exposure (ICRP Publication 26, 1977). All research involving the use of human beings requires prior approval by an ethical committee which will approve, or not, of a particular category of exposure for a particular research project according to its judgement of the balance between risk and potential benefit and according to the principles of medical ethics which are outlined. A great variety of other, non-medical or only partly medical uses of radiation is also touched on, *e.g.*, compensation claims, insurance cover, pre-employment examinations, immigration and other administrative regulations, detection of smugglers and terrorists etc.

It is stressed that "benefit" should not be interpreted in a narrow sense. It would include for example, benefits "expected to accrue in the future to patients or human beings in general" from the results of research, and benefits to the public health from screening for disease where "the interest of the community may well be of more importance in relation to particular national policies or programmes than that of the individual". The obtaining of free consent is obligatory for "almost all deliberate irradiation of human beings; the only exceptions should be applications of public health importance". The Committee is against the use of radiation in getting to know as soon as possible whether workers are affected by an industrial hazard if this is for economic reasons rather than because of individual health requirements.

Clearly this report touches on large and deep problems about which opinions are not likely to be unanimous. Perhaps doctors should ask why, as the language of the report may suggest, the public health is to be regarded as sufficiently important to justify exposing individuals to radiation risks and doing without free consent, whereas other kinds of general good, such as keeping aeroplane travel safe, are not. (But see Health aspects of Human Rights with special reference to Developments in Biology and Medicine, WHO 1976). An over-riding principle is that no practice, however small its risks, is justified if there is an alternative method of reaching the same end with less risk. Here the WHO Committee makes the interesting suggestion that in non-medical cases, say in arranging insurance cover, an individual should be given the opportunity to choose between alternative methods of examination even if his choice is for what an expert might regard as a riskier method. The second principle, given the choice of the means, is that the benefit should outweigh the risk. The WHO report makes a possibly important modification of these principles when it states that any risk resulting from a deliberate radiation exposure in Category I is *negligible* (my italics). This is surely common-sense but, like the concept of justification of risk to individuals by benefit to future generations, will not be acceptable to some because of fears about the slippery slope which might lead to unjustifiable enlargement of the range of "acceptable" risk. Moreover, this concept of negligible risk appears not to be extended to radiation exposures of similar magnitude but for purposes other than medical research.

In places the language of the report betrays what seem to me to be unwarranted anxieties about the significance of radiation damage. For example it is desirable that "the number of human beings exposed to radiation for medical research purposes should be kept under constant review" although "the proportion of the population participating in medical research involving the use of radiation is very small indeed" and "investigators should invariably obtain and review the available data on previous irradiation of the proposed participants", statements all without qualification according to category of exposure. A major criticism is that level of risk (apart from the definition of negligible) is always referred to in terms of level of dose, not in terms of kind of harm and its probability. This is surely quite unsatisfactory if free consent to a deliberate radiation exposure for research purposes involves a "proper understanding of the nature and consequence of what is proposed" and its voluntary acceptance. Moreover "the supposed radiation risks . . . should not be on a scale or of a nature to require compensation". Is this a self-evidently tenable position if malignant disease is the risk in question? And what would be the magnitude of the probability of inducing malignant disease which distinguishes negligible risk from a risk greater than negligible and which therefore requires proper understanding before free consent can be given?

The increasing occurence of "deliberate exposure of human beings to ionizing radiation apart from diagnostic and therapeutic procedures" "makes it essential to have internationally accepted guidelines on the subject". Useful, yes, and the WHO report under review is indeed most useful, but is there really a need for internationally agreed tidyness in such a matter? There are such wide differences between countries in attitudes to social purposes and to the rights of individuals that perhaps we should first make sure that we cultivate our own garden. It is disappointing to recall that there has been no lead in the UK to help ethical committees concerned with research proposals by providing anything corresponding to the WHO categories of exposure or to the concept of negligible risk. It is after all groups of individuals, such as ethical committees in the field of medical research, administrative and other committees in the field of public health etc., who have to carry the responsibilities for decisions on the great variety of particular problems. Once the general principle is accepted that benefit and risk can be balanced against each other, the guidelines to be considered may become much wider and more diverse than even a WHO expert committee can encompass.

R. H. Mole.

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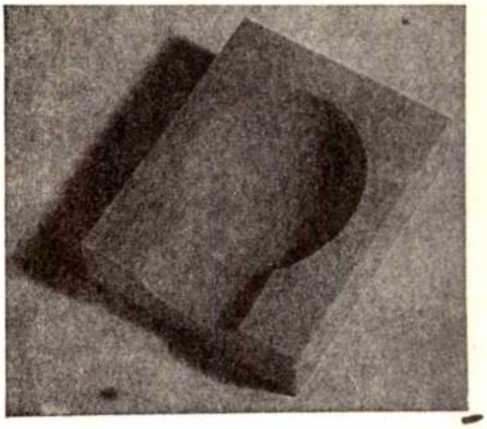

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